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Disparities by ethnicity, place of residence and human development index of infant and neonatal mortality trends in Greece during the years of economic crisis: a nationwide population study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025287
Article Type:	Research
Date Submitted by the Author:	07-Jul-2018
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Keywords:	PAEDIATRICS, Community child health < PAEDIATRICS, NEONATOLOGY, Neonatal intensive & critical care < INTENSIVE & CRITICAL CARE, EPIDEMIOLOGY, PUBLIC HEALTH

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Manuscripts

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2 **Disparities by ethnicity, place of residence and human development index of infant and**
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4 **neonatal mortality trends in Greece during the years of economic crisis: a nationwide**
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6 **population study**
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ABSTRACT**OBJECTIVE**

To explore the role of sociodemographic factors on infant (IMR) and neonatal mortality rate trends in Greece during the period 2004-2016, which includes the years of the economic crisis in the country.

DESIGN

Nationwide individual data for livebirths and infant (0-11 months) deaths provided by the Hellenic Statistical Authority (ELSTAT) were examined using Poisson regression, joinpoint regression and Interrupted Time Series (ITS) statistical analyses.

SETTING

Greece

PARTICIPANTS

All infant deaths (n=4862) over the 13-year period, of which 87.2% were born to Greek mothers, and respective livebirths.

MAIN OUTCOME MEASURES

Evolution of IMR (0-364 days), early (<7 days, ENMR)/late (7-27 days, LNMR) neonatal and post neonatal (28-364 days, PNMR) mortality trends, by maternal nationality, place of residence and Human Development Index (HDI).

RESULTS

Overall, during the study-period among infants of Greek mothers, IMR -particularly PNMR- declined significantly (-0.9%, -1.6% annually, respectively), albeit differentially by place of residence (max=IMR_{urban}:-4.1%, max=ENMR_{rural}:+24.1%). By contrast, among infants of non-Greek mothers, the low starting IMR/ENMR/LNMR/PNMR increased significantly (max ENMR:+12.5%) leading to an erroneously, non-statistically significant, positive time-trend pattern overall in Greece. The inverse associations of HDI with IMR, ENMR and PNMR were

1
2 restricted to Greek mothers' infants. Of note, joinpoint regression analyses among Greek
3
4 infants indicated sizeable, borderline significant increases of IMR following the crisis (+9.3%,
5
6 2012-2016, $p=0.07$), mainly ENMR (+10.2%, 2011-2016, $p=0.06$). By contrast, the high
7
8 (+17.1%) IMR increases among non-Greek infants were restricted to 2004-2011 and
9
10 equalized to those of Greek mothers' infants thereafter. ITS analyses in preset years (2008,
11
12 2010, 2012) overall confirmed the joinpoint results and identified adverse trends in LNMR
13
14 and PNMR after 2012 among Greek infants.
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16

17 18 **CONCLUSIONS**

19
20 HDI and rural residence were significant predictors of infant health. The strongly decreasing
21
22 IMR -especially ENMR- trends among Greeks were stagnated after a lag time of ~four years
23
24 of crisis approximating the previously sharply increasing trends among non-Greek infants.
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33 **Strengths of this study**

- 34
35 • Longest follow-up period of national data, as contrasted to previously Greek-based
36
37 studies.
- 38
39 • Moreover, maternal ethnicity is for first time considered in the analyses explaining
40
41 part, if not most, of the heterogeneity of trends through the study period.
- 42
43 • Three complimentary statistical methodologies were used to describe the overall
44
45 evolution of infant mortality and its components.
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48 **Limitations**

- 49
50 • Absence of a linkage system between birth and death data.
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52 • Data on the role of biological factors or specific causes of infant death are missing.
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Abbreviations:

IM; infant mortality

IMR; infant mortality rates

ENMR; early neonatal mortality rates

LNMR; late neonatal mortality rates

PNMR; post neonatal mortality rates

HDI; Human Development Index

ELSTAT; Hellenic Statistical Authority

ITS; Interrupted Time Series

Introduction

Socioeconomic factors have repeatedly been recognized as strong determinants of the health status of the population, including infants.¹⁻³ Economic indicators, such as the *per capita* Gross National Product, were suggested to be at least as important contributors of infant mortality (IM) as narrowly defined factors relating to provision of medical care, e.g. the relative number of doctors or hospital beds in a community.¹ Not surprisingly, the recent economic crisis of ~2008, has been linked with declines in population and child health reflected also by increased IM rates (IMR).^{4,5} It is worth noting that in European Union countries, even a minor 1% cut in government healthcare spending was associated with significant increases in all mortality metrics, including neonatal and post neonatal IM.⁶

On the contrary, associations between the crisis and increased mortality have been questioned in other studies showing that most indicators of population health, apart from those relevant to suicides and mental health, continued improving after crisis initiation.⁷⁻¹⁰ Moreover, the economic crisis has been associated with some beneficial effects, i.e. decline in rates of road traffic accidents, and smoking cessation.^{4,9} Reasonably, the impact of the crisis on health depends on several factors including the duration and intensity of the recession, the level of health care achieved prior to the recession and the type of austerity measures applied, but also on the type of the population studied with the most vulnerable groups being disproportionately affected.^{4,11,12} Due to the latter, it was proposed that studies should focus on analyzing separately the subgroups most influenced by the crisis instead of presenting results as averages in a population.⁴

Greece has been markedly affected and still suffering the recent economic crisis. Between 2008 and 2016, the country's GDP *per capita* dropped by 26%, unemployment rate increased by more than 200% (from 7.6% to 23.3%) and the median disposable income decreased by 35%.^{13,14} The GINI index, which measures income inequality, increased by 22% and the

1
2 proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016.
3
4 Total health expenditures and government expenditure on health care were both decreased
5
6 by 34% per capita over the period 2008-2016,^{13,14} whereas unmet healthcare needs
7
8 increased.¹⁵ Besides, during the last years Greece experienced large refugee flows^{16,17} with
9
10 an anticipated negative impact on the country's economy and population health indicators.
11
12 Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth
13
14 and stillbirth rates, have been also observed;^{18,19} however, sparse data exist regarding the
15
16 potential association of the crisis with IMR. It has been initially reported that during the
17
18 period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period
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20 whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to
21
22 the steady decrease observed during the preceding decade.^{20,21} Ecological correlations may
23
24 prone, however, to fallacies, whereas the different parts shaping the two main components
25
26 of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly
27
28 examined along with other factors possibly influencing the infants' health, especially
29
30 socioeconomic status and access to health care delivery.
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32 The aims of the current study were to explore time trends in early (<7 days of life) and late
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34 (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during
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36 the period 2004-2016 after taking into account nationality and place of residence, as well as
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38 changes in the Human Development Index (HDI) during the study period as a proxy of
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40 individual and collective measures of socioeconomic impact and health care access.
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50 **Materials and Methods**

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52 Following personal contact and a signed agreement, individual data for all livebirths and
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54 infant (0-11 months) deaths were provided by the Hellenic Statistical Authority (ELSTAT) for
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56 a 13-year period (2004-2016) in two separate files: one including live births and a second
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1
2 one, infant deaths; linkage of the two files was not possible as the personal identification
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4 number was not available in ELSTAT. Information on maternal demographic characteristics,
5
6 such as nationality (available since 2004) and place of residence (available till 2014), as well
7
8 as on the infants' age of death, were also provided.
9

10
11 Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late
12
13 neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective
14
15 numbers of deaths over the number of livebirths per year. Annual percent of change (APC)
16
17 during the study period were initially estimated through Poisson regression analysis using
18
19 the underlying population of each set as an offset variable. Subsequently, data were
20
21 stratified and analyzed by maternal nationality (Greek vs. non-Greek) and place of residence
22
23 (Urban/Semi-urban vs. Rural). Joinpoint regression analysis was thereafter applied to
24
25 automatically derive, through an algorithm, different segments in the mortality evolution
26
27 curves overall, as well as those by maternal nationality and place of residence. Interrupted
28
29 Time Series (ITS) analyses were also undertaken to explore the effect of crisis in alternative
30
31 years, notably 2008 indicating the maximum value of the Gross Domestic Product of the
32
33 country (Source: Aggregate National Accounts) considered to indicate the initiation of the
34
35 crisis, as well as two subsequent years notably 2010 and 2012 to control for any time lags in
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37 observing the impact of the crisis. All ITS models were checked and appropriately adjusted
38
39 for possible auto-correlation.
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46 Human development index (HDI) is a summary measure of average achievements of a
47
48 country's population in three areas including life expectancy, education and *per capita*
49
50 income indicators. Annual HDI values for the underlying populations in the year of death
51
52 were extracted from the United Nations Development Program website
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54 (<http://hdr.undp.org/en/composite/HDI>), whereas Poisson regression analysis was used to
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56 explore the association of one standard deviation of HDI with total IM and its components.
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2 All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata
3 software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13.
4
5
6 College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression
7
8 Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch,
9
10 Surveillance Research Program, National Cancer Institute).

16 **Patient involvement**

17
18 No patients were involved in setting the research question or the outcome measures, nor
19
20 were they involved in developing plans for design or implementation of the study. No
21
22 patients were asked to advise on interpretation or writing up of results. There are no plans
23
24 to disseminate the results of the research to study participants or the relevant patient
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26 community.
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32 **Ethical approval:** Not required.
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36 **Results**

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38 The annual average number of livebirths during the study period was 105077, ranging from a
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40 high 118302 (2008) to a low 91847 livebirths in 2015. The annual average proportion of
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42 Greek mothers was 83.7%, whereas the remaining were mainly economic migrants. During
43
44 the period 2004-2016, a total of 4862 infant deaths were recorded of whom 4238 (87.2%)
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46 were infants born to Greek mothers. During the early and late neonatal period, 2107 (43.3%)
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48 and 1136 (23.4%) deaths occurred, respectively, whereas another 1617 (33.3%) of deaths
49
50 were recorded in the post neonatal period. The annual average IMR was 3.5 over 1000
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52 livebirths. The corresponding figures for the early, late and post neonatal period were 1.5‰,
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54 0.8‰ and 1.2‰ respectively. Of note, in the beginning of the study period in 2004, notably
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1 well before the initiation of the crisis, IMR and its components were 2- to 4-fold higher
2 among infants born to Greek mothers in comparison with rates in infants born to non-Greek
3 origin mothers. During the subsequent 4-5 years, however, rates among Greeks followed
4 downward trends whereas among non-Greeks inflated reaching almost similar values to
5 those observed in infants born to Greek mothers (Figure 1).
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13 Overall, during the study-period, among infants born to Greek mothers, IMR, particularly
14 PNMR, declined significantly (-0.9% and -1.6% annually, respectively, $p=0.02$ for each), albeit
15 differentially by place of residence (Table 1); significant decline of IMR trends (-3.5%
16 annually, $p<0.0001$) and all its components was observed among infants born to Greek
17 mothers living in urban areas (maximum decrease in ENMR: -4.1% annually, $p<0.0001$)
18 whereas, among infants born to Greek mothers in rural areas, a significant increase of IMR
19 trend was observed (+5.2% annually, $p=0.01$) resulting mainly from increased ENMR (+24.1%
20 annually, $p<0.0001$). By contrast, among infants of non-Greek mothers, the low starting IMR
21 increased significantly by +9.4% annually ($p<0.0001$), due to significant increases of ENMR,
22 LNMR and PNMR (max ENMR: +12.5% annually, $p<0.0001$) leading to an erroneously non-
23 significant pattern of IMR evolution for Greece overall ($p=0.50$). The inverse associations of
24 HDI with IMR, ENMR and PNMR were restricted to Greek mothers' infants (Table 1).
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41 Results of joinpoint regression analyses were similar to those derived by the Poisson
42 regression apart from models displayed in Table 2 pertaining to IMR and ENMR trends.
43 Specifically, a break was identified among Greek infants restricting the decreasing IMR trend
44 to the period 2004-2012 (-4.5% annually, $p=0.01$); this was mainly due to a significant
45 decline in ENMR trend till 2011 (-6.5% annually, $p=0.02$). Of note, however, in the most
46 recent study period (2012-2016) sizeable, borderline significant increases of IMR (+9.3%
47 annually, $p=0.07$) and ENMR (+10.2% annually, $p=0.06$) were observed with no indication
48 any more of differentiation by place of residence. By contrast, among infants born to non-
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2 Greek mothers, the high IMR increases (+17.1% annually, $p=0.002$) were restricted to the
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4 period 2004-2011 with no fluctuation thereafter; finally, IMR approximated those of Greek
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6 mothers' infants.
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9 ITS analyses in the preset years 2008, 2010 and 2012 confirmed the joinpoint analysis results
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11 and further identified adverse trends in LNMR and PNMR after 2012 among Greek infants
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13 (Figure 2).
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15 16 17 18 **Discussion**

19
20 Trends of neonatal and infant mortality in Greece, spanning from year 2004 -before the
21
22 initiation of crisis in 2008- to year 2016, are not homogeneous, given significant increases in
23
24 the relatively small proportion of infants born to non-Greek nationality mothers, observed
25
26 essentially before the crisis, as contrasted to declining IMR trends among Greek infants, and
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28 increases in indices indicating differentials in proxies of health care access among Greek
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30 neonates, such as ENMR, noted ~four years after the crisis, which led to offsets of the
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32 urbanization differentials observed overall. Specifically, the “brake” of 2012 identified
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34 borderline increases of ~10% annually, thereafter, in IMR and ENMR trends among infants
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36 born to Greek mothers. Changes in HDI during the study period were also reflected in the
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38 inverse associations of ENMR and IMR, but also PNMR, among infants born to Greek
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40 mothers.
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46 Strengths of the present investigation, as contrasted to previously greek-based published
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48 studies,^{9,18,20,21,22} include the longest follow-up period of national data, namely since 2004,
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50 before the crisis, when the first data on maternal ethnicity became electronically available, to
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52 the latest available year 2016. Of great importance is also the fact that, for the first time, the
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54 maternal ethnicity was considered in the analyses explaining part, if not most, of the
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56 heterogeneity of trends through the study period. To this end, three complimentary
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2 statistical methodologies were used to describe the overall evolution depicted in Figure 1.
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4 Thus, we were able to enhance the validity of the results pertaining to the study of the
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6 evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association
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8 with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which
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10 individual data have been available on a nationwide level among both deaths and livebirths
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12 during the study period. Calculation of IMR and its components was based on the number of
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14 livebirths; yet, the absence of a linkage system between birth and death data, as well as
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16 other official registries in Greece, has not allowed use of known determinants of
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18 socioeconomic deprivation or social coherence, such as parental education,
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20 employment/occupation marital status, family income and household size. Neither were
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22 data on the role of biological factors, such as parental age, gestational age and birthweight or
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24 multiplicity of pregnancy available for both the livebirths and deaths series.^{5,19,23} Lastly,
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26 analyses by specific cause of infant death were not set among outcome measures of this
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28 study.
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34 Assessing migration as a determinant of perinatal health outcome and infant death in the
35
36 developed countries is a complex undertaking resulting in conflicting results of published
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38 studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor
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40 for unfavorable perinatal outcomes and increased neonatal and infant mortality,^{18,24-31}
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42 especially if it coincides with a financial crisis, as was the cases in Greece. Factors possibly
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44 contributing to the increased risk for poorer outcomes among children born to migrants
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46 include socioeconomic disadvantage, poor communication, discrimination, reduced
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48 utilization of health facilities, low quality of care, but also stress and consanguinity or
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50 differing attitudes to screening and termination of pregnancy associated with preterm birth,
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52 low birth weight or congenital anomalies and lethal inherited diseases.^{24,28,32-34} By contrast,
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54 other studies present similar or even better perinatal health outcomes among some migrant
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2 groups than among natives (“healthy migrant effect/paradox”).^{24-26,35,36} Refugees have been
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4 recognized as the most vulnerable group suffering increased severe neonatal morbidity and
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6 infant mortality risk,^{24,26} although no absolutely clear pattern regarding refugee or non-
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8 refugee status among migrants has been identified.³²
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11 In our study, starting rates of IMR and its components among infants born to non-Greek
12
13 mothers were lower compared to those of Greek mothers. The numbers by individual
14
15 maternal nationality were, however, small to explore the tentative influence of the changing
16
17 maternal nationality case mix during the study period. Of note, the ratio of non-Greek infants
18
19 among live births during 2009-2016 vs. 2004-2008 was only 1.32, whereas the respective
20
21 figure among infant deaths was almost 3-fold (data not shown). Indeed, a considerable
22
23 proportion of non-Greek pregnant women before the crisis were serving as home-aids in
24
25 relatively affluent Greek families, as contrasted to the adverse conditions envisaged by
26
27 pregnant women and their offspring during the most recent massive migration movements
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29 from deprived countries to European Union member states via Greece which coincided with
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31 the crisis in our country. Actually, in the pre-crisis era non-Greek mothers of newborn
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33 comprised mainly economic migrants, most of them of Albanian nationality living for many
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35 years, or even born, in Greece. After 2008, Greece experienced an unprecedented influx of
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37 refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian
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39 Territory, but also from Afghanistan, Iraq and other countries.^{16,17}
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46 The strongly decreasing IMR, especially ENMR, trends among Greek infants were stagnated
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48 after a lag time of ~four years of crisis and equalized with the previously sharply increasing
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50 trends among non-Greek maternal nationality infants; this time lag is reasonable³⁷ and in line
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52 with previous findings showing that following reductions in the government healthcare
53
54 spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was
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56 4 and 5 years later, respectively.⁶ The irony is that the period 2012-2016, during which the
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1
2 crisis was deepening^{13,14} and stricter economic austerity measures were applied,³⁸ disparities
3
4 gap in IMR trends diminished against the Greek population; IMR trends deteriorated only in
5
6 infants born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends
7
8 approached an anelastic highest value up to 2011 with no fluctuation thereafter.
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10
11 Disparities in IMR still exist across geographic areas even in well developed countries; i.e.
12
13 IMR in the United States vary by urbanization level of maternal residency being lowest in
14
15 large urban counties but highest in rural areas.³⁹ Rural women may face health challenges
16
17 related to geographic barriers to care (less timely and/or appropriate care) and physician
18
19 shortages, but they may also present differences in a number of socioeconomic and
20
21 demographic risk factors, such as less education, lower income, younger age at pregnancy,
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23 or greater number of children, in comparison with their urban counterparts.^{40,41} Disparities
24
25 in IMR trends between urban/semi urban and rural areas in Greece would not be surprising
26
27 if changes in IMR trends were observed in the same direction; the increasing IMR trends
28
29 during the study period in infants born to Greek mothers living in rural areas, as opposed to
30
31 the declining IMR trends in those born to Greek mothers living in urban/semi urban areas, is
32
33 worrisome; specific causes should be further studied and addressed. The increasing IMR
34
35 trends in infants born to non-Greek mothers despite living in urban areas can be explained
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37 by previous reports showing that other risk factors, i.e. young maternal age (<20 years) or
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39 maternal ethnic minority, may be more powerful than place of residence.⁴¹
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46 As expected, among the three IMR components, ENMR was the most “sensitive” in reflecting
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48 adverse impacts on child health as further reflected in the IMR trends. Specifically, ENMR
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50 was overall positively associated with rural place of residence of Greek children, notably
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52 before the “break” of 2012, with the increased ENMR neutralizing the urbanization
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54 differentials among newborn of Greek mothers. ENMR in developed countries, including
55
56 Greece. represents more than 70% of infant deaths on account mainly of prematurity/low
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1
2 birth weight and congenital anomalies.^{14,42-45} Actually, it reflects perinatal health and care
3
4 during pregnancy and labor, and also postnatal care in the first week of life.⁴⁴ Increased
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6 incidence of impaired perinatal parameters including low birth weight, prematurity,
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8 increased maternal age and rate of caesarian section, and also increased stillbirth rate in
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10 Greek women younger than 25 years of age, has been reported during the years of the
11
12 economic decline in Greece.^{18,19} Cuts in public health expenditures between 2008 and 2016,
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14 reduction in health care workforce and pediatric nurses, as well as reduction in the number
15
16 of obstetrics beds, obstetricians and midwives (-45.5%, -60.2% and -27.5%, respectively)¹⁴
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18 could possibly explain, at least in part, the observed increases in ENMR trends during the
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20 study period in Greece.
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25 The exact mechanisms leading to the disparities in trends of neonatal and infant mortality
26
27 observed in this study remain to be further explored. Specific maternal, family and infant
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29 features, including detailed and punctual information on the causes of infant deaths, would
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31 have shed more light on the links between IMR trends and socioeconomic factors but were
32
33 beyond the scope of this article and left for future research. Meanwhile, policies and
34
35 programs should be implemented to mitigate the negative impact of the crisis on population
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37 and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of
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39 low income, or rural place of residence, should be specifically addressed and their rights to
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41 health protected. Strong governmental integration policy for minorities paired with
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43 initiatives to improve social coherence, a deeply rooted mechanism for protection of health
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45 among those in need in the Greek society, along with improvements in primary health care
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47 delivery could help to alleviate the cost in infant lives and ensure healthy adulthood.^{30,45}
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49 Irrespective of the crisis, improvements in the quality of perinatal care, such as centralization
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51 of very preterm deliveries, establishment of regional perinatal centers, and monitoring of
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2 the implementation of evidence-based practices, could decrease ENMR and improve the
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4 perinatal indicators.⁴⁴
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8 9 REFERENCES

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11 1. Petridou E, Valadian I, Trichopoulos D, Tzonou A, Kyriopoulos Y, Matsaniotis N. Medical
12 services and socioeconomic factors: Determinants of infant mortality in Greece. *Hygie*
13 1989;3:20-3.
14
15 2. WHO. The determinants of health. [http://www. who.int/hia/evidence/doh/en](http://www.who.int/hia/evidence/doh/en) (Date of
16 access: 30/5/2018)
17
18 3. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England
19 compared with Sweden: a birthcohort study. *Lancet* 2018;391(10134):2008-2018.
20 doi:10.1016/S0140-6736(18)30670-6.
21
22 4. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al; International Network for
23 Research in Inequalities in Child Health (INRICH). Impact of the 2008 economic and financial
24 crisis on child health: a systematic review. *Int J Environ Res Public Health* 2014;11:6528-46.
25 doi:10.3390/ijerph110606528.
26
27 5. Glonti K, Gordeev VS, Goryakin Y, Reeves A, Stuckler D, McKee M, Roberts B. A systematic
28 review on health resilience to economic crises. *PLoS One* 2015;10:e0123117.
29 doi:10.1371/journal.pone.0123117.
30
31 6. Budhdeo S, Watkins J, Atun R, Williams C, Zeltner T, Maruthappu M. Changes in
32 government spending on healthcare and population mortality in the European union, 1995–
33 2010: a cross-sectional ecological study. *J R Soc Med* 2015;108:490-8.
34 doi:10.1177/0141076815600907.
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60
7. Tapia Granados JA, Rodriguez JM. Health, economic crisis, and austerity: A comparison of Greece, Finland and Iceland. *Health Policy* 2015;119:941-53. doi:10.1016/j.healthpol.2015.04.009.
8. Regidor E, Barrio G, Bravo MJ, de la Fuente L. Has health in Spain been declining since the economic crisis? *J Epidemiol Community Health* 2014;68:280-2. doi:10.1136/jech-2013-202944.
9. Laliotis I, Ioannidis JPA, Stavropoulou C. Total and cause-specific mortality before and after the onset of the Greek economic crisis: an interrupted time-series analysis. *Lancet Public Health* 2016;1: e56–e65. doi:10.1016/S2468-2667(16)30018-4.
10. Parmar D, Stavropoulou C, Ioannidis JP. Health outcomes during the 2008 financial crisis in Europe: systematic literature review. *BMJ* 2016;354:i4588. doi:10.1136/bmj.i4588.
11. O'Donnell C, Burns N, Dowrick C, Lionis C, MacFarlane A; RESTORE team. Health-care access for migrants in Europe. *Lancet* 2013; 382:393. doi: 10.1016/S0140-6736(13)61666-9.
12. Karanikolos M, Heino P, McKee M, Stuckler D, Legido-Quigley H. Effects of the Global Financial Crisis on Health in High-Income OECD Countries: A Narrative Review. *Int J Health Serv* 2016;46:208-40. doi: 10.1177/0020731416637160.
13. Organisation for Economic Co-operation and Development OECD data. <https://data.oecd.org> (Date of access: 30/5/2018) (2016).
14. Hellenic Statistical Authority *Statistics*. www.statistics.gr (Date of access: 30/5/2018) (2016).
15. Zavras D, Zavras AI, Kyriopoulos II, Kyriopoulos J. Economic crisis, austerity and unmet healthcare needs: the case of Greece. *BMC Health Serv Res* 2016;16:309. doi:10.1186/s12913-016-1557-5.
16. European Union. The EU and the migration crisis, July 2017, <http://publications.europa.eu>

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17. Mertens E, Rockenschaub G, Economopoulou A, Kreidl P. Assessment of public health issues of migrants at the Greek-Turkish border, April 2011. *Euro Surveill* 2012 Jan 12;17(2). pii: 20056.
18. Zografaki I, Papamichail D, Panagiotopoulos T. Adverse effect of the financial crisis in Greece on perinatal factors. *Eur J Public Health* 2018 [Epub ahead of print]. doi: 10.1093/eurpub/cky078.
19. Sdoná E, Papamichail D, Ragkou E, Briana DD, Malamitsi-Puchner A, Panagiotopoulos T. Greek economic crisis and impaired perinatal parameters: experience from a public maternity hospital. *J Matern Fetal Neonatal Med* 2018;31:2371-5. doi:10.1080/14767058.2017.1342803.
20. Michas G, Varytimiadi A, Chasiotis I, Micha R. Maternal and child mortality in Greece. *Lancet* 2014;383:691-2. doi:10.1016/S0140-6736(14)60251-8.
21. Filippidis F, Gerovasili V, Millett C, Tountas Y. Medium-term impact of the economic crisis on mortality, health-related behaviours and access to healthcare in Greece. *Sci Rep* 2017;7:46423. doi:10.1038/srep46423.
22. Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in Greece in the literature from 2009 to 2013: a systematic review. *Health Policy* 2014;115:111-9. doi: 10.1016/j.healthpol.2014.02.002.
23. Petridou ET, Georgakis MK, Erdmann F, et al. Advanced parental age as risk factor for childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia International Consortium. *Eur J Epidemiol* 2018. doi:10.1007/s10654-018-0402-z. [Epub ahead of print].
24. Gissler M, Alexander S, MacFarlane A, et al. Stillbirths and infant deaths among migrants in industrialized countries. *Acta Obstet Gynecol Scand* 2009;88:134-48. doi:10.1080/00016340802603805.

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25. Gagnon AJ, Zimbeck M, Zeitlin J, et al. Migration to western industrialized countries and perinatal health: a systematic review. *Soc Sci Med* 2009;69:934-46. doi:10.1016/j.socscimed.2009.06.027.
26. Wanigaratne S, Cole DC, Bassil K, et al. Severe Neonatal Morbidity Among Births to Refugee Women. *Matern Child Health J* 2016;20:2189-98. doi:10.1007/s10995-016-2047-4.
27. Puthussery S. Perinatal outcomes among migrant mothers in the United Kingdom: Is it a matter of biology, behaviour, policy, social determinants or access to health care? *Best Pract Res Clin Obstet Gynaecol* 2016;32:39-49. doi:10.1016/j.bpobgyn.2015.09.003.
28. Wanner P, Bollini P. The contribution of the foreign population to the high level of infant mortality in Switzerland: a demographic analysis. *BMC Pregnancy Childbirth* 2017;17:151. doi:10.1186/s12884-017-1332-6.
29. Cantarutti A, Franchi M, Monzio Compagnoni M, Merlino L, Corrao G. Mother's education and the risk of several neonatal outcomes: an evidence from an Italian population-based study. *BMC Pregnancy Childbirth* 2017;17:221. doi:10.1186/s12884-017-1418-1.
30. Bollini P, Pampallona S, Wanner P, Kupelnick B. Pregnancy outcome of migrant women and integration policy: a systematic review of the international literature. *Soc Sci Med* 2009;68:452-61. doi:10.1016/j.socscimed.2008.10.018.
31. Gotsens M, Malmusi D, Villarroel N, et al. Health inequality between immigrants and natives in Spain: the loss of the healthy immigrant effect in times of economic crisis. *Eur J Public Health* 2015;25:923-9. doi:10.1093/eurpub/ckv126.
32. Nybo Andersen AM, Gundlund A, Villadsen SF. Stillbirth and congenital anomalies in migrants in Europe. *Best Pract Res Clin Obstet Gynaecol* 2016;32:50-9. doi:10.1016/j.bpobgyn.2015.09.004.

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33. Di Renzo GC, Tosto V, Giardina I. The biological basis and prevention of preterm birth. *Best Pract Res Clin Obstet Gynaecol* 2018. doi:10.1016/j.bpobgyn.2018.01.022. [Epub ahead of print].
34. Wanigaratne S, Cole DC, Bassil K, Hyman I, Moineddin R, Urquia ML. The influence of refugee status and secondary migration on preterm birth. *J Epidemiol Community Health* 2016;70:622-8. doi:10.1136/jech-2015-206529.
35. Kirby RS. Perinatal outcomes and nativity: does place of birth really influence infant health? *Birth* 2011;38:354-6. doi:10.1111/j.1523-536X.2011.00505.x.
36. Sdoná E, Papamichail D, Ragkou E, et al. Migration status and perinatal parameters in a Greek public maternity hospital: an illustration of the "healthy immigrant effect". *J Matern Fetal Neonatal Med* 2017. doi: 10.1080/14767058.2017.1371131. [Epub ahead of print].
37. Karanikolos M, Mladovsky P, Cylus J, et al. Financial crisis, austerity, and health in Europe. *Lancet* 2013;381:1323-31. doi:10.1016/S0140-6736(13)60102-6.
38. Burki T. Health under austerity in Greece. *Lancet* 2018;391:525-6. doi:10.1016/S0140-6736(18)30242-3.
39. Ely DM, Driscoll AK, Mathews TJ. Infant mortality rates in rural and urban areas in the United States, 2014. *NCHS data brief*, No 285. Hyattsville, MD: National Center for Health Statistics, 2017.
40. Van de Poel E, O'Donnell O, Van Doorslaer E. What explains the rural-urban gap in infant mortality: household or community characteristics? *Demography* 2009;46:827-50. doi:org/10.1353/dem.0.0074.
41. Harris DE, Aboueissa AM, Baugh N, Sarton C. Impact of rurality on maternal and infant health indicators and outcomes in Maine. *Rural Remote Health* 2015;15:3278.
42. Heron M. Deaths: Leading Causes for 2015. *Natl Vital Stat Rep* 2017;66:1-76.

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43. Roncancio CP, Misnaza SP, Peña IC, Prieto FE, Cannon MJ, Valencia D. Trends and characteristics of fetal and neonatal mortality due to congenital anomalies, Colombia 1999-2008. *J Matern Fetal Neonatal Med* 2018;31:1748-55. doi:10.1080/14767058.2017.1326901.
44. Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: A challenge worldwide. *Semin Fetal Neonatal Med* 2017;22:153-60. doi:10.1016/j.siny.2017.02.006.
45. Alexander M, Harding M, Lamarche C. Quantifying the impact of economic crises on infant mortality in advanced economies. *Applied Economics* 2011; 43: 3313–23. doi:10.1080/00036840903559620.

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2 **Contributors:** EP and GC were involved in the initial conception of the study. All authors
3
4 contributed to the design, analysis and interpretation of data. TS, ND and EP developed the
5
6 first draft of the manuscript and all authors critically revised it and approved the final
7
8 version. All authors agree to be accountable for all aspects of the work in ensuring that
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10 questions related to the accuracy or integrity of any part of the work are appropriately
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12 investigated and resolved. The corresponding author ensures that all the journal's
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14 administrative requirements are properly completed.
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18 ELSTAT has provided individual anonymized data.
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23 **Data sharing:** No additional data available.
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27 **Funding Statement**

28
29 This research received no specific grant from any funding agency in the public, commercial
30
31 or not-for-profit sectors'
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36 **Competing interests statement**

37
38 All authors have completed the ICMJE uniform disclosure form at
39
40 www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the
41
42 submitted work; no financial relationships with any organizations that might have an interest
43
44 in the submitted work in the previous three years; no other relationships or activities that
45
46 could appear to have influenced the submitted work.
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Figure Legends

Figure 1. Infant, Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

Figure 2. Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) by maternal nationality in alternative years of interest (2008, 2010 and 2012)

Figure 2A) infants born to Greek mothers; Figure 2B) infants born to Non-Greek mothers

Table 1. Poisson regression derived changes and 95% Confidence Intervals (CI) of infant (IMR), early (ENMR), late (LNMR) and postneonatal mortality rates (PNMR) in time periods with available data: Annual Percent of Change (APC) for place of residence (2004-2014) and maternal nationality (2004-2016); Percent of Change (PC) for 1 Standard Deviation of Human Development Index (HDI, 2000-2015) controlling for year.

Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	-0.9 (-1.7,-0.1)	0.02	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	-1.6 (-3.0,-0.2)	0.02
Non-Greek	615	9.4 (6.9,11.9)	<.0001	258	12.5 (8.6,16.5)	<.0001	138	8.0 (3.1,13.2)	0.001	218	4.4 (0.6,8.4)	0.02
Any*	4862	0.3 (-0.5, 1.0)	0.50	2107	0.9 (-0.3,2.1)	0.13	1136	0.4 (-1.2,2.0)	0.65	1617	-0.9 (-2.2,0.5)	0.20
Urbanization												
Urban-Semi urban												
Greek	3305	-3.5 (-4.6, -2.4)	<.0001	1476	-4.1 (-5.7, -2.5)	<.0001	781	-2.7 (-4.9, -0.5)	0.02	1048	-3.3 (-5.2, -1.4)	0.001
Non-Greek	494	13.3 (9.9, 16.9)	<.0001	208	19.4 (13.7, 25.3)	<.0001	110	11.2 (4.2, 18.6)	0.001	176	8.2 (2.8, 13.8)	0.002
Any*	3807	-1.6 (-2.6, -0.6)	0.002	1684	-1.7 (-3.2, -0.1)	0.03	894	-1.2 (-3.3, 0.9)	0.27	1229	-1.8 (-3.6, 0.0)	0.05
Rural												
Greek	275	5.2 (1.3, 9.3)	0.01	69	24.1 (14.2, 34.8)	<.0001	62	4.6 (-3.4, 13.3)	0.27	144	-2 (-7.1, 3.3)	0.44
Non-Greek	22	-6.9 (-19.4, 7.5)	0.33	7	14.8 (-8.0, 43.3)	0.22	3	-1.9 (34.7, 47.4)	0.93	12	-12.4 (-32.0, 12.9)	0.31
Any*	298	4.3 (0.6, 8.2)	0.02	76	24.4 (14.8, 34.7)	<.0001	65	3.6 (-4.2, 12.1)	0.38	157	-3.4 (-8.2, 1.6)	0.18
HDI												
PC			PC			PC			PC			
Greek		-8.6 (-14.8, -1.9)	0.01		-11.3 (-20.8, -1.4)	0.03		3.5 (-10.9, 20.1)	0.66		-12.3 (-22.2, -1.2)	0.03
Non-Greek		-5.7 (-25.0, 18.7)	0.62		-19.8 (-44.8, 16.6)	0.25		20.0 (-28.6, 101.7)	0.49		-1.3 (-30.7, 40.5)	0.94
Any*		-9.5 (15.3, -3.2)	0.004		-14.0 (-22.3, -4.7)	0.004		3.3 (-10.4, 19.3)	0.65		-11.4 (-20.8, -0.7)	0.04

*including missing maternal nationality values

Table 2. Joinpoint regression derived Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant (IMR) and early neonatal mortality rates (ENMR) by maternal nationality (only for indices showing breaks in the time period examined).

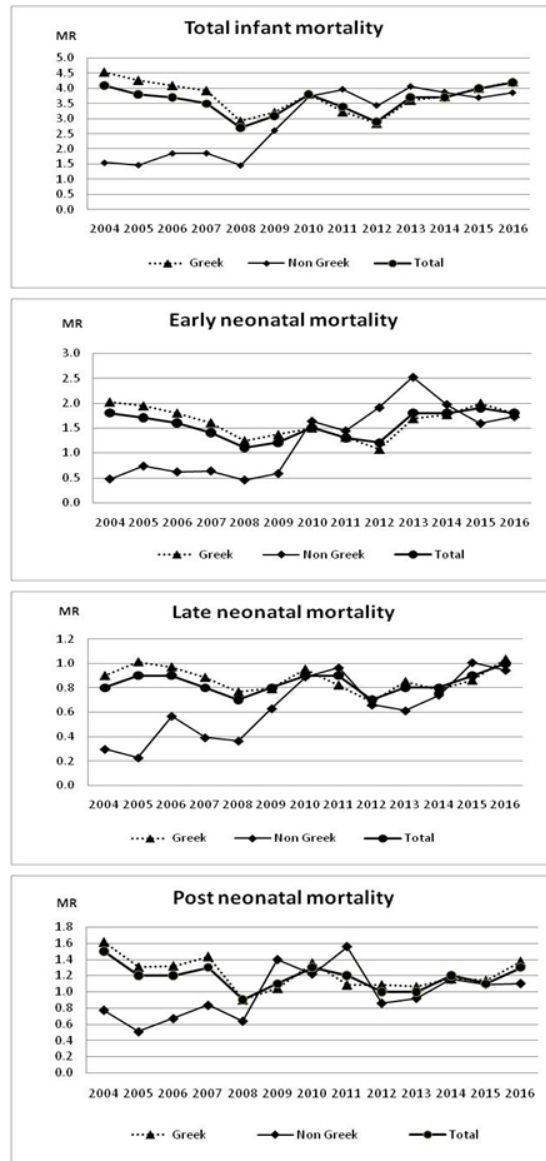
Variable	Years	N	IMR APC (95% CI)	p-value	Time period	N	ENMR APC (95% CI)	p-value
Greek	2004-12	2870	-4.5 (-7.6, -1.3)	0.01	2004-11	1118	-6.5 (-11.4, -1.4)	0.02
	2012-16	1368	9.3 (-1.1, 20.9)	0.07	2011-16	731	10.2 (-0.4, 21.9)	0.06
Non-Greek	2004-11	333	17.1 (8.1, 26.9)	0.002				
	2011-16	282	0.2 (-11.5, 13.5)	0.97				
Any*	2004-08	1807	-7.5(-14.6, 0.3)	0.06	2004-08	780	-10.7 (-19.9, -0.5)	0.04
	2008-16	3055	3.6 (0.7, 6.6)	0.02	2008-16	1327	6.1 (2.1, 10.3)	0.01

* Including missing maternal nationality values

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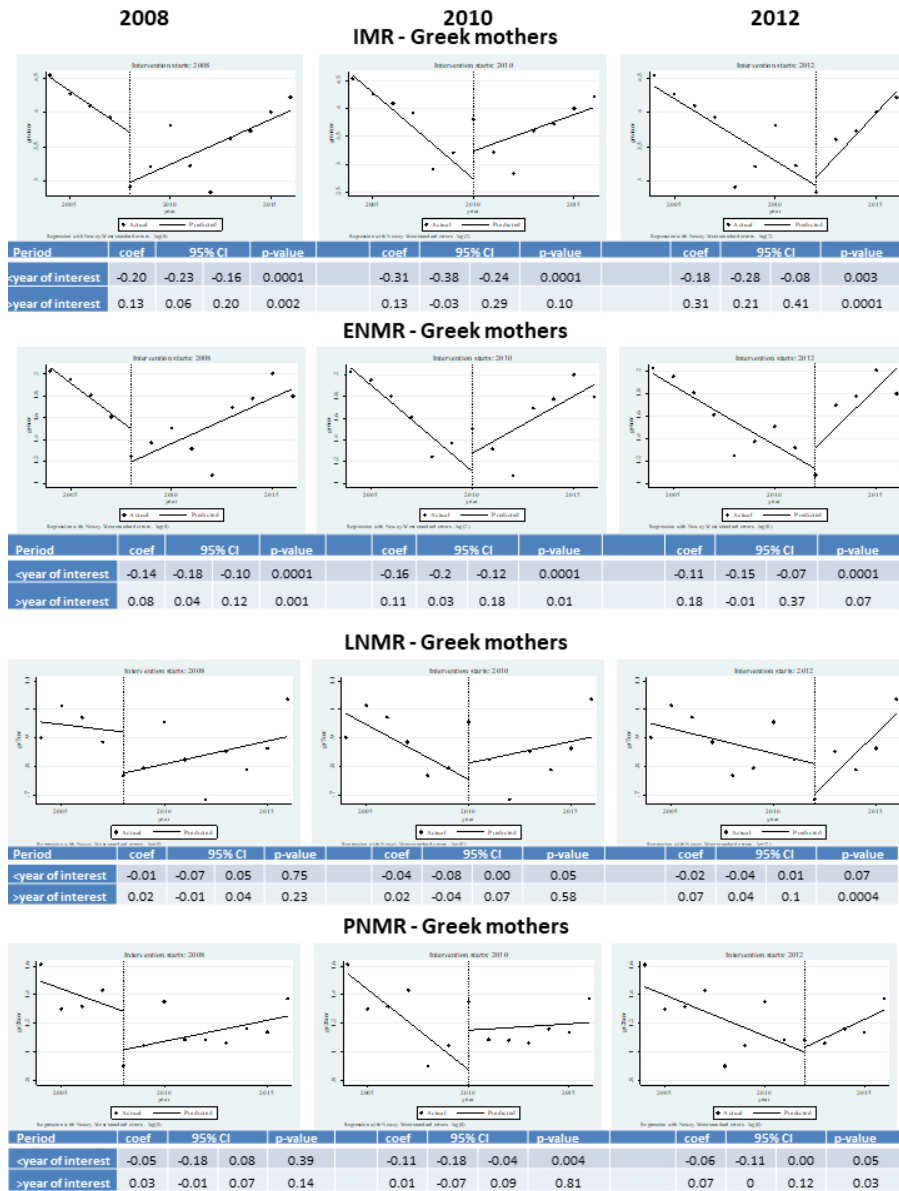
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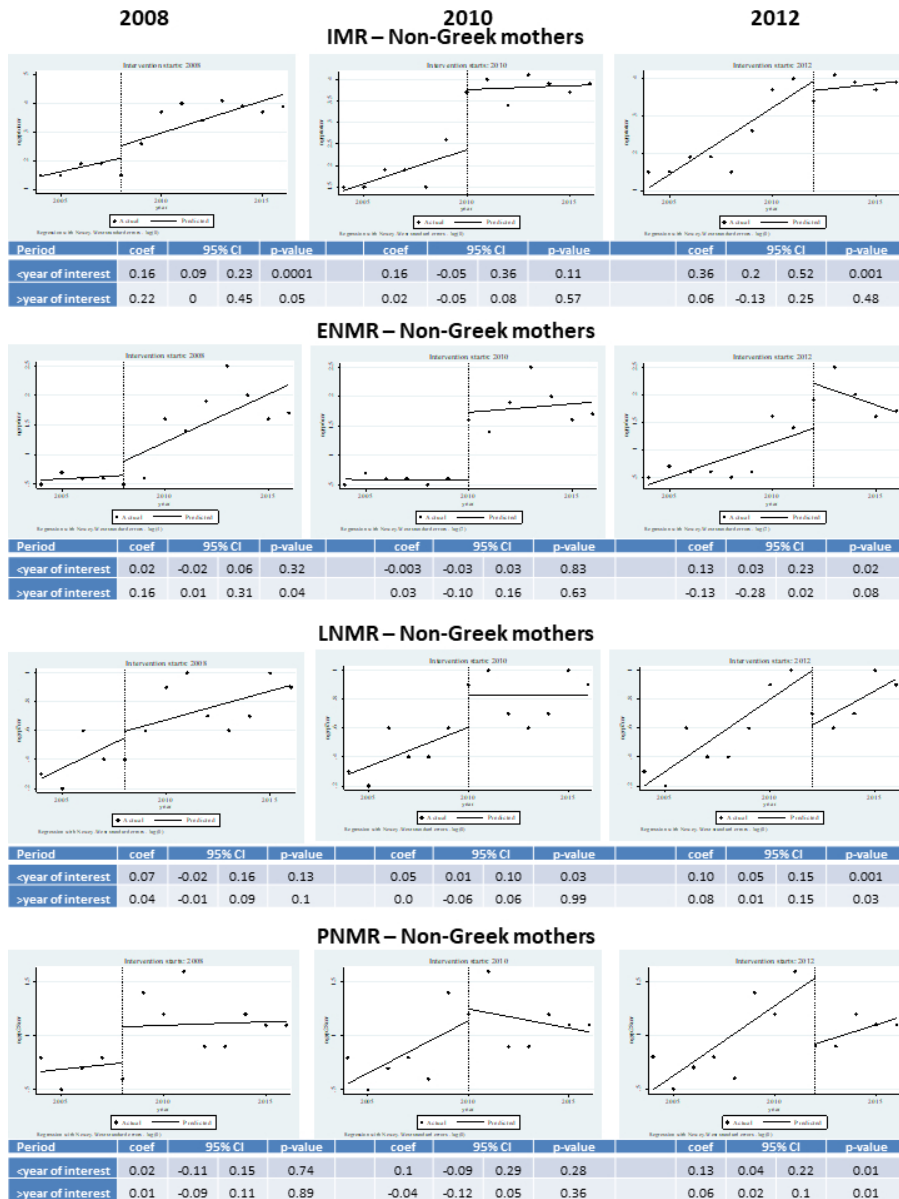
Infant, Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

190x254mm (96 x 96 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) by maternal nationality in alternative years of interest (2008, 2010 and 2012) in infants born to Greek mothers

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190x254mm (96 x 96 DPI)

Research checklist- STROBE Statement—checklist

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Participants	6	7-8
Variables	7	7-8
Data sources/ measurement	8*	7-8
Bias	9	N/A
Study size	10	N/A
Quantitative variables	11	7-8
Statistical methods	12	8-9
Results		
Participants	13*	9-10
Descriptive data	14*	9-10
Outcome data	15*	10=11
Main results	16	10-11
Other analyses	17	N/A
Discussion		
Key results	18	11
Limitations	19	12
Interpretation	20	12-14
Generalisability	21	15
Other information		
Funding	22	21

BMJ Open

Disparities of infant and neonatal mortality trends in Greece during the years of economic crisis by ethnicity, place of residence and human development index: a nationwide population study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025287.R1
Article Type:	Research
Date Submitted by the Author:	19-Oct-2018
Complete List of Authors:	Siahanidou, Tania; First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine Dessypris, Nick; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens Analitis, Antonis; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens Mihas, Constantinos; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens Evangelou, Evangelos; Dept of Hygiene and Epidemiology; Department of Epidemiology and Biostatistics, Imperial College Chrousos, George; First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine PETRIDOU, ELENI; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens; Clinical Epidemiology Unit, Karolinska Institute, 171 77
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health, Health policy, Global health
Keywords:	Neonates, Mortality rates, Infant deaths, perinatal care, financial crisis

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2 **Disparities of infant and neonatal mortality trends in Greece during the years of economic**
3 **crisis by ethnicity, place of residence and human development index: a nationwide population**
4 **study**
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ABSTRACT**OBJECTIVE**

To study trends of infant (IMR) and neonatal mortality rate in Greece during the period 2004-2016 and explore the role of sociodemographic factors in the years of crisis

DESIGN

Nationwide individual data for livebirths and infant (0-11 months) deaths provided by the Hellenic Statistical Authority (ELSTAT) were examined using Poisson regression, joinpoint regression and Interrupted Time Series (ITS) statistical analyses.

SETTING

Greece

PARTICIPANTS

All infant deaths (n=4862) over the 13-year period, of which 87.2% were born to Greek mothers, and respective livebirths.

MAIN OUTCOME MEASURES

Evolution of IMR (0-364 days), early (<7 days, ENMR)/late (7-27 days, LNMR) neonatal and post neonatal (28-364 days, PNMR) mortality trends, by maternal nationality, place of residence and Human Development Index (HDI).

RESULTS

Overall, during the study-period among infants of Greek mothers, IMR -particularly PNMR- declined significantly (-0.9%, -1.6% annually, respectively), albeit differentially by place of residence (max=IMR_{urban}: -4.1%, max=ENMR_{rural}: +24.1%). By contrast, among infants of non-Greek mothers, the low starting IMR/ENMR/LNMR/PNMR increased significantly (max ENMR: +12.5%) leading to an erroneously, non-statistically significant, positive time-trend pattern

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2 overall in Greece. The inverse associations of HDI with IMR, ENMR and PNMR were restricted to
3
4 Greek mothers' infants. Of note, joinpoint regression analyses among Greek infants indicated
5
6 sizeable, borderline significant increases of IMR following the crisis (+9.3%, 2012-2016, $p=0.07$),
7
8 mainly ENMR (+10.2%, 2011-2016, $p=0.06$). By contrast, the high (+17.1%) IMR increases among
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10 non-Greek infants were restricted to 2004-2011 and equalized to those of Greek mothers'
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12 infants thereafter. ITS analyses in preset years (2008, 2010, 2012) overall confirmed the
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14 joinpoint results and identified adverse trends in LNMR and PNMR after 2012 among Greek
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16 infants.
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22 **CONCLUSIONS**

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24 HDI and rural residence were significantly associated with IMR. The strongly decreasing IMR -
25
26 especially ENMR- trends among Greeks were stagnated after a lag time of ~four years of crisis
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28 approximating the previously sharply increasing trends among non-Greek infants.
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37 **Strengths of this study**

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39 • Longest follow-up period of national data, as contrasted to previously Greek-based
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41 studies.
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- 44 • Maternal ethnicity is for first time considered in the analyses explaining part, if not most,
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46 of the heterogeneity of trends through the study period.
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- 49 • Three complimentary statistical methodologies were used to describe the overall
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51 evolution of infant mortality and its components.
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54 **Limitations**

- 55
56 • Absence of a linkage system between birth and death data.
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- Data on the role of biological factors or specific causes of infant death are missing.

Abbreviations:

IM; infant mortality

IMR; infant mortality rates

ENMR; early neonatal mortality rates

LNMR; late neonatal mortality rates

PNMR; post neonatal mortality rates

HDI; Human Development Index

ELSTAT; Hellenic Statistical Authority

ITS; Interrupted Time Series

Introduction

Socioeconomic factors have repeatedly been recognized as strong determinants of the health status of the population, including infants.¹⁻³ Economic indicators, such as the *per capita* Gross National Product, were suggested to be at least as important contributors of infant mortality (IM) as narrowly defined factors relating to provision of medical care, e.g. the relative number of doctors or hospital beds in a community.¹ Not surprisingly, the recent economic crisis of ~2008, has been linked with declines in population and child health reflected also by increased IM rates (IMR).^{4,5} It is worth noting that in European Union countries, even a minor 1% cut in government healthcare spending was associated with significant increases in all mortality metrics, including neonatal and post neonatal IM.⁶

On the contrary, associations between the crisis and increased mortality have been questioned in other studies showing that most indicators of population health, apart from those relevant to suicides and mental health, continued improving after crisis initiation.⁷⁻¹⁰ Moreover, the economic crisis has been associated with some beneficial effects, i.e. decline in rates of road traffic accidents, and smoking cessation.^{4,9} Reasonably, the impact of the crisis on health depends on several factors including the duration and intensity of the recession, the level of health care achieved prior to the recession and the type of austerity measures applied, but also on the type of the population studied with the most vulnerable groups being disproportionately affected.^{4,11,12} Due to the latter, it was proposed that studies should focus on analyzing separately the subgroups most influenced by the crisis instead of presenting results as averages in a population.⁴

Greece has been markedly affected and still suffering the recent economic crisis. Between 2008 and 2016, the country's GDP *per capita* dropped by 26%, unemployment rate increased by more

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3 than 200% (from 7.6% to 23.3%) and the median disposable income decreased by 35%.^{13,14} The
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5 GINI index, which measures income inequality, increased by 22% and the proportion of
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7 individuals at risk of poverty or social exclusion climbed to almost 36% in 2016. Total health
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9 expenditures and government expenditure on health care were both decreased by 34% per
10
11 capita over the period 2008-2016,^{13,14} whereas unmet healthcare needs increased.¹⁵ Besides,
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13 during the last years, Greece experienced large refugee flows^{16,17} with an anticipated negative
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15 impact on the country's economy and population health indicators. Adverse effects of financial
16
17 crisis on perinatal factors, such as low birth weight, preterm birth and stillbirth rates, have been
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19 also observed;^{18,19} however, sparse data exist regarding the potential association of the crisis
20
21 with IMR. It has been initially reported that during the period 2003-2012, IMR in Greece did not
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23 differ between the pre-crisis and crisis period whereas, a later study showed that IMR increased
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25 between 2010 and 2015 as contrasted to the steady decrease observed during the preceding
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27 decade.^{20,21} Ecological correlations may prone, however, to fallacies, whereas the different parts
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29 shaping the two main components of IM, namely neonatal (NM) and post neonatal mortality
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31 (PNM), should have been distinctly examined along with other factors possibly influencing the
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33 infants' health, especially socioeconomic status and access to health care delivery.
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41 The aims of the current study were to explore time trends in early (<7 days of life) and late (7-27
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43 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during the
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45 period 2004-2016 after taking into account nationality and place of residence, as well as
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47 changes in the Human Development Index (HDI) during the study period as a proxy of individual
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49 and collective measures of socioeconomic impact and health care access.
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56 **Materials and Methods**

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3 Following personal contact and a signed agreement, individual data for all livebirths and infant
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5 (0-11 months) deaths were provided by the Hellenic Statistical Authority (ELSTAT) for a 13-year
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7 period (2004-2016) in two separate files: one including live births and a second one, infant
8
9 deaths; linkage of the two files was not possible as the personal identification number was not
10
11 available in ELSTAT. Information on maternal demographic characteristics, such as nationality
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13 (available for years 2004-2016) and place of residence (available for years 2004-2014), as well as
14
15 on the infants' age of death, were also provided.
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19 Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal
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21 (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of
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23 deaths over the number of livebirths per year. Annual percent of change (APC) during the study
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25 period was initially estimated through Poisson regression analysis using the underlying
26
27 population of each set as an offset variable. Subsequently, data were stratified and analyzed by
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29 maternal nationality (Greek vs. non-Greek) and place of residence (Urban/Semi-urban vs. Rural).
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31 Joinpoint regression analysis²² was thereafter applied to automatically derive, through an
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33 algorithm, different segments in the mortality evolution curves overall, as well as those by
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35 maternal nationality and place of residence. Interrupted Time Series (ITS) analyses were also
36
37 undertaken as a sensitivity analysis to further explore the effect of crisis on IMR and its
38
39 components in alternative prespecified years, notably 2008, considered to indicate the initiation
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41 of the crisis in Greece as the value of the Gross Domestic Product of the country was maximum
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43 at that year but dropped afterwards (Source: Aggregate National Accounts), and in two successive
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45 periods two years apart (2010 and 2012), to control for possible time lags in observing the impact
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47 of the crisis. All ITS models were verified and appropriately adjusted for possible auto-
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49 correlation; autoregressive integrated moving-average models were used to control for
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2 autocorrelation and to estimate treatment effects over multiple periods. In our ITS analysis a
3 slope “<year of interest” is fitted until the introduction of the crisis, “>year of interest” represents
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5 the change in the level of the mortality immediately following the initiation of the crisis and
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7 “change of slope” represents the differences between pre and post crisis intervention slopes.
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11 Human development index (HDI) is a summary measure of average achievements of a country's
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13 population in three areas including life expectancy, education and *per capita* income indicators.
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15 Annual HDI values for the underlying populations in the year of death were extracted from the
16
17 United Nations Development Program website (<http://hdr.undp.org/en/composite/HDI>),
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19 whereas Poisson regression analysis was used to explore the association of one standard
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21 deviation of HDI with total IM and its components. All statistical analyses were performed using
22
23 the SAS software (V9.4, SAS Institute Inc.), Stata software program, version 13 (StataCorp. 2013.
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25 Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and Joinpoint
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27 Regression Program (Joinpoint Regression Program, Version 4.5.0.1 - June 2017; Statistical
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29 Methodology and Applications Branch, Surveillance Research Program, National Cancer
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31 Institute).
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41 **Patient involvement**

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43 No patients were involved in setting the research question or the outcome measures, nor were
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45 they involved in developing plans for design or implementation of the study. No patients were
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47 asked to advise on interpretation or writing up of results. There are no plans to disseminate the
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49 results of the research to study participants or the relevant patient community.
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56 **Ethical approval:** Not required.
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Results

The annual average number of livebirths during the study period was 105077, ranging from a high 118302 (2008) to a low 91847 livebirths in 2015. The annual average proportion of Greek mothers was 83.7%, whereas the remaining were mainly economic migrants. During the period 2004-2016, a total of 4862 infant deaths were recorded of whom 4238 (87.2%) were of infants born to Greek mothers, whereas among the remaining 615 deaths of infants born to non-Greek mothers, 298 (48.5%) were of infants born to Albanian mothers, 146 (23.7%) of infants born to mothers from Balkan countries and countries of the former Soviet Union, 77 (12.5%) from Asia, 47 (7.6%) from countries of the European Union or other developed countries and 47 (7.6%) from Africa. During the early and late neonatal period, 2107 (43.3%) and 1136 (23.4%) deaths occurred, respectively, whereas another 1617 (33.3%) of deaths were recorded in the post neonatal period. The annual average IMR was 3.5 over 1000 livebirths, whereas the corresponding figures for the early, late and post neonatal period were 1.5‰, 0.8‰ and 1.2‰ respectively. The number of livebirths and infant deaths, as well as total IMR per 1000 livebirths in infants born to Greek and non-Greek mothers, in Greece, during the study period, are shown in Table 1.

Of note, in the beginning of the study period in 2004, notably well before the initiation of the crisis, IMR and its components were 2- to 4-fold higher among infants born to Greek mothers in comparison with rates in infants born to non-Greek origin mothers. During the subsequent 4-5 years, however, rates among Greeks followed downward trends whereas among non-Greeks inflated reaching almost similar values to those observed in infants born to Greek mothers (Figure 1).

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2 Overall, during the study-period, among infants born to Greek mothers, IMR, particularly PNMR,
3 declined significantly (-0.9% and -1.6% annually, respectively, $p=0.02$ for each), albeit
4 differentially by place of residence (Table 2); significant decline of IMR trends (-3.5% annually,
5 $p<0.0001$) and all its components was observed among infants born to Greek mothers living in
6 urban areas (maximum decrease in ENMR: -4.1% annually, $p<0.0001$) whereas, among infants
7 born to Greek mothers in rural areas, a significant increase of IMR trend was observed (+5.2%
8 annually, $p=0.01$) resulting mainly from increased ENMR (+24.1% annually, $p<0.0001$). By
9 contrast, among infants of non-Greek mothers, the low starting IMR increased significantly by
10 +9.4% annually ($p<0.0001$), due to significant increases of ENMR, LNMR and PNMR (max ENMR:
11 +12.5% annually, $p<0.0001$) leading to an erroneously non-significant pattern of IMR evolution
12 for Greece overall ($p=0.50$). Inverse associations of HDI with IMR, ENMR and PNMR, restricted
13 to Greek mothers' infants, were observed (Table 2).

14
15 In order to examine whether IMR, in our study population, might have influenced by any
16 variation in the registration of births in cases of uncertain viability, we analyzed separately the
17 infant deaths in the first day of life; trends of IMR in this age group, over the study period, were
18 non-significant (average annual percent change: -1.22%; 95% CI: -3.79% to 1.42%; $p=0.36$).

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20 Results of joinpoint regression analyses were similar to those derived by the Poisson regression
21 apart from models displayed in Table 3 pertaining to IMR and ENMR trends. Specifically, a
22 break was identified among Greek infants restricting the decreasing IMR trend to the period
23 2004-2012 (-4.5% annually, $p=0.01$); this was mainly due to a significant decline in ENMR trend
24 till 2011 (-6.5% annually, $p=0.02$). Of note, however, in the most recent study period (2012-
25 2016) sizeable, borderline significant, increases of IMR (+9.3% annually, $p=0.07$) and ENMR
26 (+10.2% annually, $p=0.06$) were observed with no indication any more of differentiation by

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2 place of residence. By contrast, among infants born to non-Greek mothers, the high IMR
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4 increases (+17.1% annually, $p=0.002$) were restricted to the period 2004-2011 with no
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6 fluctuation thereafter; finally, IMR approximated those of Greek mothers' infants (Table 3).
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10 ITS analyses in the preset years 2008, 2010 and 2012 (Figures 2 and 3) confirmed the joinpoint
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12 analysis results and further identified adverse trends in LNMR and PNMR after 2012 among
13
14 Greek infants (Figure 2).
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16 17 18 19 **Discussion**

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21 Trends of neonatal and infant mortality in Greece, spanning from year 2004 -before the
22
23 initiation of crisis in 2008- to year 2016, are not homogeneous, given significant increases in the
24
25 relatively small proportion of infants born to non-Greek nationality mothers as contrasted to
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27 declining IMR trends among Greek infants, and increases in indices indicating differentials in
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29 proxies of health care access among Greek neonates, such as ENMR, noted ~four years after the
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31 crisis, which led to offsets of the urbanization differentials observed overall. Specifically, the
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33 "brake" of 2012 identified borderline increases of ~10% annually, thereafter, in IMR and ENMR
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35 trends among infants born to Greek mothers. Changes in HDI during the study period were also
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37 reflected in the inverse associations of HDI with ENMR and IMR, but also PNMR, among infants
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39 born to Greek mothers.
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47 Strengths of the present investigation, as contrasted to previously Greek-based published
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49 studies,^{9,18,20,21,23} include the longest follow-up period of national data, namely since 2004,
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51 before the crisis, when the first data on maternal ethnicity became electronically available, to
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53 the latest available year 2016. Of great importance is also the fact that, for the first time, the
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55 maternal ethnicity was considered in the analyses explaining part, if not most, of the
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3 heterogeneity of trends through the study period. To this end, three complimentary statistical
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5 methodologies were used to describe the overall evolution depicted in Figure 1. Thus, we were
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7 able to enhance the validity of the results pertaining to the study of the evolution of individual
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9 IMR components, namely ENMR, LNMR and PNMR, in association with socioeconomic factors
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11 (i.e maternal nationality, place of residence and HDI) for which individual data have been
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13 available on a nationwide level among both deaths and livebirths during the study period.
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15 Calculation of IMR and its components was based on the number of livebirths; yet, the absence
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17 of a linkage system between birth and death data, as well as other official registries in Greece,
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19 has not allowed use of known determinants of socioeconomic deprivation or social coherence,
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21 such as parental education, employment/occupation, marital status, family income and
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23 household size. Neither were data on the role of biological factors, such as parental age,
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25 gestational age and birthweight or multiplicity of pregnancy available for both the livebirths and
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27 deaths series.^{5,19,24} Besides, the study period, with available information on maternal nationality
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29 and place of residence, was rather short leading to ITS analyses with few data points; ITS
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31 analysis can be used even for few observations; no log-transformation is needed but the results
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33 should be interpreted with caution as the power depends on various factors.²⁵ Lastly, analyses by
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35 specific cause of infant death were not set among the outcome measures of this study.
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44 Assessing migration as a determinant of perinatal health outcome and infant death in the
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46 developed countries is a complex undertaking resulting in conflicting results of published
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48 studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor for
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50 unfavorable perinatal outcomes and increased neonatal and infant mortality,^{18,26-33} especially if
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52 it coincides with a financial crisis, as was the case in Greece. Factors possibly contributing to the
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54 increased risk for poorer outcomes among children born to migrants include socioeconomic
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3 disadvantage, poor communication, discrimination, reduced utilization of health facilities, low
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5 quality of care, but also stress and consanguinity or differing attitudes to screening and
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7 termination of pregnancy associated with preterm birth, low birth weight or congenital
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9 anomalies and lethal inherited diseases.^{26,30,34-36} By contrast, other studies present similar or
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11 even better perinatal health outcomes among some migrant groups than among natives
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13 (“healthy migrant effect/paradox”).^{26-28,37,38} Refugees have been recognized as the most
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15 vulnerable group suffering increased severe neonatal morbidity and infant mortality risk,^{26,28}
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17 although no absolutely clear pattern regarding refugee or non-refugee status among migrants
18
19 has been identified.³⁴

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24 In our study, starting rates of IMR and its components among infants born to non-Greek
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26 mothers were lower compared to those of Greek mothers. The numbers by individual maternal
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28 nationality were, however, small to explore the tentative influence of the changing maternal
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30 nationality case mix during the study period; this issue needs to be further followed-up by other
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32 types of research methodology. Of note, the ratio of non-Greek infants among live births during
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34 2009-2016 vs. 2004-2008 was only 1.32, whereas the respective figure among infant deaths was
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36 almost 3-fold (data not shown). Indeed, a considerable proportion of non-Greek pregnant
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38 women before the crisis were serving as home-aids in relatively affluent Greek families, as
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40 contrasted to the adverse conditions envisaged by pregnant women and their offspring during
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42 the most recent massive migration movements from deprived countries to European Union
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44 member states via Greece which coincided with the crisis in our country. Actually, in the pre-
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46 crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most of them
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48 of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece
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50 experienced an influx of refugees with the majority of them fleeing from war and terror in Syria,
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3 Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.^{16,17} It could
4
5 be suggested that changes in the homogeneity of foreign mothers during the study period, in
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7 association with the country's economic difficulties, might have led from the "healthy migrant
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9 effect", observed before 2008, to the deterioration of IM indicators and IMR trends, afterwards,
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11 in infants born to non-Greek mothers.
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15 Simultaneously with immigration to/through Greece, the country experienced the third wave of
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17 mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left Greece since the
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19 onset of the economic crisis, in 2008, seeking new opportunities and employment in other
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21 countries, mainly Germany, the United Kingdom and the Netherlands.^{39,40} The current
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23 emigration wave of Greeks involved mostly highly-educated people (the so called "brain-drain")
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25 of young age, leading to a decrease in the number of Greek women of childbearing age.⁴¹ This
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27 fact, along with the decrease in the fertility rate by almost 10% between 2008 and 2016,
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29 contributes significantly to the reduction in the annual number of livebirths in Greece by almost
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31 23% during the period of the economic crisis.^{41,42} Furthermore, the flow of mostly affluent and
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33 well educated people going outside Greece might have also contributed, to a certain extent, to
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35 the observed increases in IMR among Greek children following the crisis.
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43 The strongly decreasing IMR, especially ENMR, trends among Greek infants were stagnated
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45 after a lag time of ~four years of crisis and equalized with the previously sharply increasing
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47 trends among non-Greek maternal nationality infants; this time lag is reasonable⁴³ and in line
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49 with previous findings showing that following reductions in the government healthcare
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51 spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4
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53 and 5 years later, respectively.⁶ The irony is that the period 2012-2016, during which the crisis
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55 was deepening^{13,14} and stricter economic austerity measures were applied,⁴⁴ disparities gap in
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3 IMR trends diminished against the Greek population; IMR trends deteriorated only in infants
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5 born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends approached
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7 an anelastic highest value up to 2011 with no fluctuation thereafter. The importance of two sub-
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9 analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized;
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11 when trends in the entire study population were assessed, year 2008, considered the year of crisis
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13 initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint
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15 regression analysis, in line with findings of previous relevant studies in Greece which did not
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17 take into consideration the maternal nationality.²⁰

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22 Disparities in IMR still exist across geographic areas even in well developed countries; i.e. IMR in
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24 the United States vary by urbanization level of maternal residency being lowest in large urban
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26 counties but highest in rural areas.⁴⁵ Rural women may face health challenges related to
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28 geographic barriers to care (less timely and/or appropriate care) and physician shortages, but
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30 they may also present differences in a number of socioeconomic and demographic risk factors,
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32 such as less education, lower income, younger age at pregnancy, or greater number of children,
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34 in comparison with their urban counterparts.^{46,47} Disparities in IMR trends between urban/semi
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36 urban and rural areas in Greece would not be surprising if changes in IMR trends were observed
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38 in the same direction; the increasing IMR trends during the study period in infants born to
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40 Greek mothers living in rural areas, as opposed to the declining IMR trends in those born to
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42 Greek mothers living in urban/semi urban areas, is worrisome; specific causes should be further
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44 studied and addressed. The increasing IMR trends in infants born to non-Greek mothers despite
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46 living in urban areas can be explained by previous reports showing that other risk factors, i.e.
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48 young maternal age (<20 years) or maternal ethnic minority, may be more powerful than place
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50 of residence.⁴⁷

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3 As expected, among the three IMR components, ENMR was the most “sensitive” in reflecting
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5 adverse impacts on child health as further reflected in the IMR trends. Specifically, ENMR was
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7 overall positively associated with rural place of residence of Greek children, notably before the
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9 “break” of 2012, with the increased ENMR neutralizing the urbanization differentials among
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11 newborns of Greek mothers. ENMR, in developed countries, including Greece, represents more
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13 than 70% of neonatal deaths on account mainly of prematurity/low birth weight and congenital
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15 anomalies.^{14,48-51} Actually, it reflects perinatal health and care during pregnancy and labor, and
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17 also postnatal care in the first week of life.⁵⁰ Increased incidence of impaired perinatal
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19 parameters including low birth weight, prematurity, and increased maternal age and rate of
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21 caesarian section, have been reported during the years of the economic decline in Greece.^{18,19}
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27 Cuts in public health expenditures between 2008 and 2016, reduction in health care workforce
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29 and pediatric nurses, as well as reduction in the number of obstetrics beds, obstetricians and
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31 midwives (-45.5%, -60.2% and -27.5%, respectively)¹⁴ could possibly explain, at least in part, the
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33 observed increases in ENMR trends during the study period in Greece. Besides, it is worth
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35 mentioning that IMR and ENMR are influenced by variation in the registration of births in case of
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37 uncertain viability.⁵² In Greece, like in other countries,⁵³ misclassification in reporting of
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39 extremely preterm births of <24 weeks of gestation, as live or stillborn, may exist. Further
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41 analysis of IMR trends after excluding extremely preterm births would be useful to minimize any
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43 registration variation; however, as mentioned in the limitations of this study, gestational age data
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45 of the study population are missing. To clarify this issue we analyzed separately the infant deaths
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47 in the first day of life; trends of IMR in this age group, over the study period, were non-
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49 significant (average annual percent change: -1.22%; 95% CI: -3.79% to 1.42%; p=0.36).
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55 The exact mechanisms leading to the disparities in trends of neonatal and infant mortality
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57 observed in this study remain to be further explored. Specific maternal, family and infant
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2 features, including detailed and punctual information on the causes of infant deaths, would
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4 have shed more light on the links between IMR trends and socioeconomic factors but were
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6 beyond the scope of this article and left for future research. Meanwhile, policies and programs
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8 should be implemented to mitigate the negative impact of the crisis on population and infant
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10 health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of low income,
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12 or rural place of residence, should be specifically addressed and their rights to health protected.
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14 Barriers in the access of refugees to the Greek health care system have been mostly related to
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16 language, culture, and inadequate information about the healthcare system, but also include
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18 difficulties in the coordination of Health Services, transportation problems, issues in obtaining
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20 expertise medical assessment in the camps, lack of continuity of care, financial difficulties in
21
22 making out-of-pocket payments for health and social care services, and administrative barriers,
23
24 among others.⁵⁴ In response, the Greek government and several Non-Governmental
25
26 Organizations initiated commendable actions, i.e. National Health System services free of
27
28 charge for uninsured and vulnerable social groups including asylum seekers , translation services
29
30 in public hospitals, access to specialist care/treatment with Gynecologists (mostly women),
31
32 midwives, dentists, psychologists, and psychiatrists being lately included in the camp clinics;⁵⁴
33
34 these actions may have prevented deterioration of IMR which are being kept at steady levels
35
36 after 2011 in infants of non-Greek mothers; efforts should be continued and intensified,
37
38 however, as to ensure equity with local populations. Strong governmental integration policy for
39
40 minorities paired with initiatives to improve social coherence, a deeply rooted mechanism for
41
42 protection of health among those in need in the Greek society, along with further
43
44 improvements in primary health care delivery could help to alleviate the cost in infant lives and
45
46 ensure healthy adulthood.^{32,51} Irrespective of the crisis, improvements in the quality of perinatal
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2 and neonatal care, including centralization of very preterm deliveries, establishment of regional
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4 perinatal centers, monitoring of the implementation of evidence-based practices in maternity
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6 and neonatal units, as well as increase in health expenditures, health care workforce, number of
7
8 doctors and midwives/nurses, could decrease ENMR, eventually leading to overall decrease in
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12 IMR in Greece.⁵⁰
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20 REFERENCES

- 21
22 1. Petridou E, Valadian I, Trichopoulos D, Tzonou A, Kyriopoulos Y, Matsaniotis N. Medical
23
24 services and socioeconomic factors: Determinants of infant mortality in Greece. *Hygie*
25
26 1989;3:20-3.
27
28
29 2. WHO. The determinants of health. <http://www.who.int/hia/evidence/doh/en> (Date of access:
30
31 30/5/2018)
32
33
34 3. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England compared
35
36 with Sweden: a birthcohort study. *Lancet* 2018;391(10134):2008-2018. doi:10.1016/S0140-
37
38 6736(18)30670-6.
39
40
41 4. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al; International Network for Research
42
43 in Inequalities in Child Health (INRICH). Impact of the 2008 economic and financial crisis on child
44
45 health: a systematic review. *Int J Environ Res Public Health* 2014;11:6528-46.
46
47 doi:10.3390/ijerph110606528.
48
49
50 5. Glonti K, Gordeev VS, Goryakin Y, Reeves A, Stuckler D, McKee M, Roberts B. A systematic
51
52 review on health resilience to economic crises. *PLoS One* 2015;10:e0123117.
53
54
55
56 doi:10.1371/journal.pone.0123117.
57
58
59
60

- 1
2
3 6. Budhdeo S, Watkins J, Atun R, Williams C, Zeltner T, Maruthappu M. Changes in government
4
5 spending on healthcare and population mortality in the European union, 1995–2010: a cross-
6
7 sectional ecological study. *J R Soc Med* 2015;108:490-8. doi:10.1177/0141076815600907.
8
- 9
10 7. Tapia Granados JA, Rodriguez JM. Health, economic crisis, and austerity: A comparison of
11
12 Greece, Finland and Iceland. *Health Policy* 2015;119:941-53.
13
14 doi:10.1016/j.healthpol.2015.04.009.
15
- 16
17 8. Regidor E, Barrio G, Bravo MJ, de la Fuente L. Has health in Spain been declining since the
18
19 economic crisis? *J Epidemiol Community Health* 2014;68:280-2. doi:10.1136/jech-2013-202944.
20
- 21
22 9. Laliotis I, Ioannidis JPA, Stavropoulou C. Total and cause-specific mortality before and after
23
24 the onset of the Greek economic crisis: an interrupted time-series analysis. *Lancet Public Health*
25
26 2016;1: e56–e65. doi:10.1016/S2468-2667(16)30018-4.
27
- 28
29 10. Parmar D, Stavropoulou C, Ioannidis JP. Health outcomes during the 2008 financial crisis in
30
31 Europe: systematic literature review. *BMJ* 2016;354:i4588. doi:10.1136/bmj.i4588.
32
- 33
34 11. O'Donnell C, Burns N, Dowrick C, Lionis C, MacFarlane A; RESTORE team. Health-care access
35
36 for migrants in Europe. *Lancet* 2013; 382:393. doi: 10.1016/S0140-6736(13)61666-9.
37
- 38
39 12. Karanikolos M, Heino P, McKee M, Stuckler D, Legido-Quigley H. Effects of the Global
40
41 Financial Crisis on Health in High-Income OECD Countries: A Narrative Review. *Int J Health Serv*
42
43 2016;46:208-40. doi: 10.1177/0020731416637160.
44
- 45
46 13. Organisation for Economic Co-operation and Development OECD data.
47
48 <https://data.oecd.org> (Date of access: 30/5/2018) (2016).
49
- 50
51 14. Hellenic Statistical Authority *Statistics*. www.statistics.gr (Date of access: 30/5/2018) (2016).
52
53
54
55
56
57
58
59
60

- 1
2
3 15. Zavras D, Zavras AI, Kyriopoulos II, Kyriopoulos J. Economic crisis, austerity and unmet
4 healthcare needs: the case of Greece. *BMC Health Serv Res* 2016;16:309. doi:10.1186/s12913-
5 016-1557-5.
6
7
8
9
10 16. European Union. The EU and the migration crisis, July 2017, <http://publications.europa.eu>
11
12 17. Mertens E, Rockenschaub G, Economopoulou A, Kreidl P. Assessment of public health issues
13 of migrants at the Greek-Turkish border, April 2011. *Euro Surveill* 2012 Jan 12;17(2). pii: 20056.
14
15 18. Zografaki I, Papamichail D, Panagiotopoulos T. Adverse effect of the financial crisis in Greece
16 on perinatal factors. *Eur J Public Health* 2018 [Epub ahead of print]. doi:
17 10.1093/eurpub/cky078.
18
19 19. Sdoná E, Papamichail D, Ragkou E, Briana DD, Malamitsi-Puchner A, Panagiotopoulos T.
20 Greek economic crisis and impaired perinatal parameters: experience from a public maternity
21 hospital. *J Matern Fetal Neonatal Med* 2018;31:2371-5. doi:10.1080/14767058.2017.1342803.
22
23 20. Michas G, Varytimiadi A, Chasiotis I, Micha R. Maternal and child mortality in Greece. *Lancet*
24 2014;383:691-2. doi:10.1016/S0140-6736(14)60251-8.
25
26 21. Filippidis F, Gerovasili V, Millett C, Tountas Y. Medium-term impact of the economic crisis on
27 mortality, health-related behaviours and access to healthcare in Greece. *Sci Rep* 2017;7:46423.
28 doi:10.1038/srep46423.
29
30 22. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
31 applications to cancer rates. *Stat Med* 2000;19:335-51. PMID:10649300
32
33 23. Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in Greece
34 in the literature from 2009 to 2013: a systematic review. *Health Policy* 2014;115:111-9. doi:
35 10.1016/j.healthpol.2014.02.002.
36
37
38
39
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43
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45
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47
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49
50
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53
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57
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59
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- 1
2
3 24. Petridou ET, Georgakis MK, Erdmann F, et al. Advanced parental age as risk factor for
4 childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia
5 International Consortium. *Eur J Epidemiol* 2018. doi:10.1007/s10654-018-0402-z. [Epub ahead
6 of print].
7
8
9
10
11
12 25. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of
13 public health interventions: a tutorial. *Int J Epidemiol* 2017;46(1):348-55. doi:
14 10.1093/ije/dyw098.
15
16
17
18
19 26. Gissler M, Alexander S, MacFarlane A, et al. Stillbirths and infant deaths among migrants in
20 industrialized countries. *Acta Obstet Gynecol Scand* 2009;88:134-48.
21 doi:10.1080/00016340802603805.
22
23
24
25
26
27 27. Gagnon AJ, Zimbeck M, Zeitlin J, et al. Migration to western industrialized countries and
28 perinatal health: a systematic review. *Soc Sci Med* 2009;69:934-46.
29 doi:10.1016/j.socscimed.2009.06.027.
30
31
32
33
34 28. Wanigaratne S, Cole DC, Bassil K, et al. Severe Neonatal Morbidity Among Births to Refugee
35 Women. *Matern Child Health J* 2016;20:2189-98. doi:10.1007/s10995-016-2047-4.
36
37
38
39 29. Puthussery S. Perinatal outcomes among migrant mothers in the United Kingdom: Is it a
40 matter of biology, behaviour, policy, social determinants or access to health care? *Best Pract*
41 *Res Clin Obstet Gynaecol* 2016;32:39-49. doi:10.1016/j.bpobgyn.2015.09.003.
42
43
44
45
46 30. Wanner P, Bollini P. The contribution of the foreign population to the high level of infant
47 mortality in Switzerland: a demographic analysis. *BMC Pregnancy Childbirth* 2017;17:151.
48 doi:10.1186/s12884-017-1332-6.
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 31. Cantarutti A, Franchi M, Monzio Compagnoni M, Merlino L, Corrao G. Mother's education
4 and the risk of several neonatal outcomes: an evidence from an Italian population-based study.
5 *BMC Pregnancy Childbirth* 2017;17:221. doi:10.1186/s12884-017-1418-1.
6
7
8
9
10 32. Bollini P, Pampallona S, Wanner P, Kupelnick B. Pregnancy outcome of migrant women and
11 integration policy: a systematic review of the international literature. *Soc Sci Med* 2009;68:452-
12
13
14
15 61. doi:10.1016/j.socscimed.2008.10.018.
16
17 33. Gotsens M, Malmusi D, Villarroel N, et al. Health inequality between immigrants and natives
18 in Spain: the loss of the healthy immigrant effect in times of economic crisis. *Eur J Public Health*
19
20
21
22 2015;25:923-9. doi:10.1093/eurpub/ckv126.
23
24 34. Nybo Andersen AM, Gundlund A, Villadsen SF. Stillbirth and congenital anomalies in
25 migrants in Europe. *Best Pract Res Clin Obstet Gynaecol* 2016;32:50-9.
26
27
28
29
30
31
32 35. Di Renzo GC, Tosto V, Giardina I. The biological basis and prevention of preterm birth. *Best*
33
34
35
36
37 36. Wanigaratne S, Cole DC, Bassil K, Hyman I, Moineddin R, Urquia ML. The influence of
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
37. Kirby RS. Perinatal outcomes and nativity: does place of birth really influence infant health?
Birth 2011;38:354-6. doi:10.1111/j.1523-536X.2011.00505.x.
38. Sdoná E, Papamichail D, Ragkou E, et al. Migration status and perinatal parameters in a
Greek public maternity hospital: an illustration of the "healthy immigrant effect". *J Matern Fetal
Neonatal Med* 2017. doi: 10.1080/14767058.2017.1371131. [Epub ahead of print].

- 1
2
3 39. Eurostat, "Emigration by age group, sex and citizenship".
4
5 http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=migr_emi1ctz&lang=en (last
6
7 updated: 04/04/2018).
8
9
10 40. Cavounidis J. The changing face of emigration: Harnessing the potential of the New Greek
11
12 Diaspora. Washington, DC: Migration Policy Institute, 2015.
13
14 41. Vrachnis N, Vlachadis N, Iliodromiti Z, Vlachadi M, Creatsas G. Greece's birth rates and the
15
16 economic crisis. *Lancet* 2014;383:692-3. doi: 10.1016/S0140-6736(14)60252-X.
17
18 42. Eurostat, "Fertility indicators". [http://appsso.eurostat.ec.europa.eu/nui/show.](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en)
19
20 [do?dataset=demo_find&lang=en](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en) (last updated: 20/09/2018)
21
22
23 43. Karanikolos M, Mladovsky P, Cylus J, et al. Financial crisis, austerity, and health in Europe.
24
25 *Lancet* 2013;381:1323-31. doi:10.1016/S0140-6736(13)60102-6.
26
27
28 44. Burki T. Health under austerity in Greece. *Lancet* 2018;391:525-6. doi:10.1016/S0140-
29
30 6736(18)30242-3.
31
32
33 45. Ely DM, Driscoll AK, Mathews TJ. Infant mortality rates in rural and urban areas in the United
34
35 States, 2014. *NCHS data brief*, No 285. Hyattsville, MD: National Center for Health Statistics,
36
37 2017.
38
39
40 46. Van de Poel E, O'Donnell O, Van Doorslaer E. What explains the rural-urban gap in infant
41
42 mortality: household or community characteristics? *Demography* 2009;46:827-50.
43
44 doi:org/10.1353/dem.0.0074.
45
46
47 47. Harris DE, Aboueissa AM, Baugh N, Sarton C. Impact of rurality on maternal and infant
48
49 health indicators and outcomes in Maine. *Rural Remote Health* 2015;15:3278.
50
51
52 48. Heron M. Deaths: Leading Causes for 2015. *Natl Vital Stat Rep* 2017;66:1-76.
53
54
55
56
57
58
59
60

- 1
2
3 49. Roncancio CP, Misnaza SP, Peña IC, Prieto FE, Cannon MJ, Valencia D. Trends and
4 characteristics of fetal and neonatal mortality due to congenital anomalies, Colombia 1999-
5 2008. *J Matern Fetal Neonatal Med* 2018;31:1748-55. doi:10.1080/14767058.2017.1326901.
6
7
8
9
10 50. Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: A challenge
11 worldwide. *Semin Fetal Neonatal Med* 2017;22:153-60. doi:10.1016/j.siny.2017.02.006.
12
13
14 51. Alexander M, Harding M, Lamarche C. Quantifying the impact of economic crises on infant
15 mortality in advanced economies. *Applied Economics* 2011; 43: 3313–23.
16 doi:10.1080/00036840903559620.
17
18
19
20 52. Smith L, Draper ES, Manktelow BN, Pritchard C, Field DJ. Comparing regional infant death
21 rates: the influence of preterm births <24 weeks of gestation. *Arch Dis Child Fetal Neonatal Ed*
22 2013;98:F103-7. doi:10.1136/fetalneonatal-2011-301359
23
24
25
26 53. Smith LK, Blondel B, Van Reempts P, et al. Variability in the management and outcomes of
27 extremely preterm births across five European countries: a population-based cohort study. *Arch*
28 *Dis Child Fetal Neonatal Ed* 2017;102:F400-8. doi: 10.1136/archdischild-2016-312100.
29
30
31
32 54. Kotsiou OS, Kotsios P, Srivastava DS, Kotsios V, Gourgoulialis KI, Exadaktylos AK. Impact of
33 the Refugee Crisis on the Greek Healthcare System: A Long Road to Ithaca. *Int J Environ Res*
34 *Public Health* 2018;15(8). pii:E1790. doi: 10.3390/ijerph15081790.
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49 **Contributors:** EP and GC were involved in the initial conception of the study. All authors
50 contributed to the design, analysis and interpretation of data. TS, ND and EP developed the first
51 draft of the manuscript and all authors critically revised it and approved the final version. ND,
52 AA and CM performed the statistical analyses; EE reviewed statistics and contributed
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2 significantly for ITS analyses. All authors agree to be accountable for all aspects of the work in
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4 ensuring that questions related to the accuracy or integrity of any part of the work are
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6 appropriately investigated and resolved. The corresponding author ensures that all the journal's
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8 administrative requirements are properly completed.
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15 **Acknowledgements:** ELSTAT has provided individual anonymized data.
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20 **Data sharing:** No additional data available.
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24

25 **Funding Statement**

26
27 This research received no specific grant from any funding agency in the public, commercial or
28
29 not-for-profit sectors'
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35 **Competing interests statement**

36
37 All authors have completed the ICMJE uniform disclosure form at
38
39 www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the
40
41 submitted work; no financial relationships with any organizations that might have an interest in
42
43 the submitted work in the previous three years; no other relationships or activities that could
44
45 appear to have influenced the submitted work.
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Figure Legends

Figure 1. Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

Figure 2. Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to Greek mothers.

Figure 3. Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to non-Greek mothers.

Table 1. Livebirths, infant deaths and total infant mortality rates (IMR) per 1000 livebirths in infants born to Greek and non-Greek mothers in Greece during the period 2004-2016

Year	Infants born to Greek mothers			Infants born to non-Greek mothers		
	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths
2004	88805	403	4.5	16825	26	1.5
2005	89819	383	4.3	17678	26	1.5
2006	92590	379	4.1	19396	36	1.9
2007	91462	359	3.9	20412	38	1.9
2008	96329	281	2.9	21931	32	1.5
2009	95640	307	3.2	22244	58	2.6
2010	93209	355	3.8	21351	80	3.7
2011	87445	282	3.2	18680	74	4.0
2012	84868	241	2.8	15153	52	3.4
2013	80938	292	3.6	13063	53	4.1
2014	79985	298	3.7	12144	47	3.9
2015	79919	320	4.0	11919	44	3.7
2016	80166	338	4.2	12721	49	3.9

*excluding missing maternal nationality values

Table 2. Poisson regression derived changes and 95% Confidence Intervals (CI) of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in time periods with available data: Annual Percent of Change (APC) for place of residence (2004-2014) and maternal nationality (2004-2016); Percept of Change (PC) for 1 Standard Deviation of Human Development Index (HDI, 2000-2015) controlling for year of birth.

Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	-0.9 (-1.7,-0.1)	0.02	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	-1.6 (-3.0,-0.2)	0.02
Non-Greek	615	9.4 (6.9,11.9)	<.0001	258	12.5 (8.6,16.5)	<.0001	138	8.0 (3.1,13.2)	0.001	218	4.4 (0.6,8.4)	0.02
All*	4862	0.3 (-0.5, 1.0)	0.50	2107	0.9 (-0.3,2.1)	0.13	1136	0.4 (-1.2,2.0)	0.65	1617	-0.9 (-2.2,0.5)	0.20
Urbanization												
Urban-Semi urban												
Greek	3305	-3.5 (-4.6, -2.4)	<.0001	1476	-4.1 (-5.7, -2.5)	<.0001	781	-2.7 (-4.9, -0.5)	0.02	1048	-3.3 (-5.2, -1.4)	0.001
Non-Greek	494	13.3 (9.9, 16.9)	<.0001	208	19.4 (13.7, 25.3)	<.0001	110	11.2 (4.2, 18.6)	0.001	176	8.2 (2.8, 13.8)	0.002
Any*	3807	-1.6 (-2.6, -0.6)	0.002	1684	-1.7 (-3.2, -0.1)	0.03	894	-1.2 (-3.3, 0.9)	0.27	1229	-1.8 (-3.6, 0.0)	0.05
Rural												
Greek	275	5.2 (1.3, 9.3)	0.01	69	24.1 (14.2, 34.8)	<.0001	62	4.6 (-3.4, 13.3)	0.27	144	-2.0 (-7.1, 3.3)	0.44
Non-Greek	22	-6.9 (-19.4, 7.5)	0.33	7	14.8 (-8.0, 43.3)	0.22	3	-1.9 (-34.7, 47.4)	0.93	12	-12.4 (-32.0, 12.9)	0.31
All*	298	4.3 (0.6, 8.2)	0.02	76	24.4 (14.8, 34.7)	<.0001	65	3.6 (-4.2, 12.1)	0.38	157	-3.4 (-8.2, 1.6)	0.18
HDI												
PC			PC			PC			PC			
Greek		-8.6 (-14.8, -1.9)	0.01		-11.3 (-20.8, -1.4)	0.03		3.5 (-10.9, 20.1)	0.66		-12.3 (-22.2, -1.2)	0.03
Non-Greek		-5.7 (-25.0, 18.7)	0.62		-19.8 (-44.8, 16.6)	0.25		20.0 (-28.6, 101.7)	0.49		-1.3 (-30.7, 40.5)	0.94
All*		-9.5 (15.3, -3.2)	0.004		-14.0 (-22.3, -4.7)	0.004		3.3 (-10.4, 19.3)	0.65		-11.4 (-20.8, -0.7)	0.04

*including missing maternal nationality values

Table 3. Joinpoint regression derived Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant (IMR) and early neonatal mortality rates (ENMR) by maternal nationality (only for indices showing breaks in the time period examined).

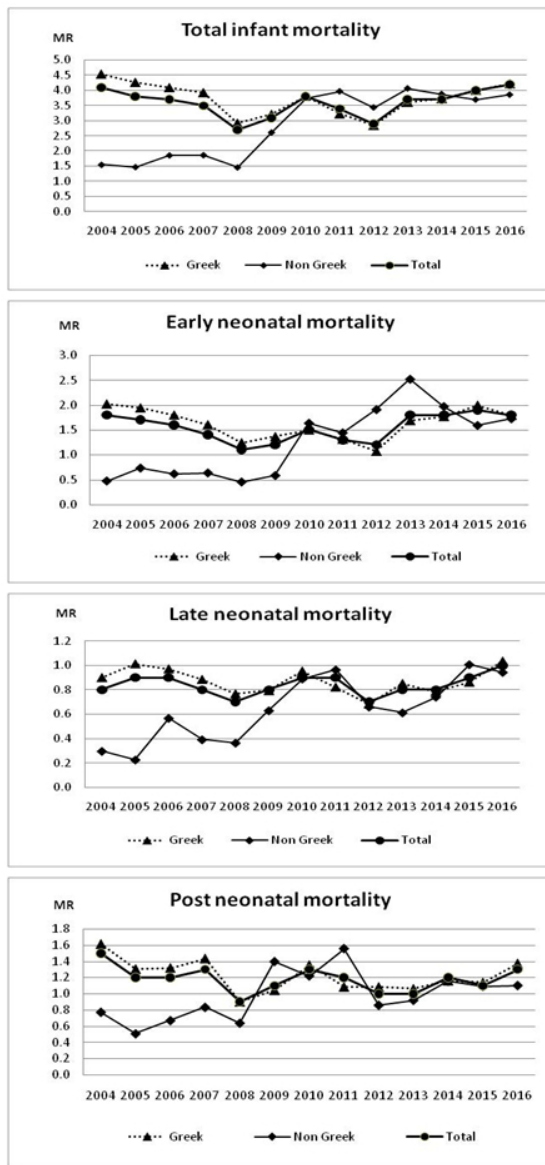
Variable	Years	N	IMR APC (95% CI)	p-value	Time period	N	ENMR APC (95% CI)	p-value
Greek	2004-12	2870	-4.5 (-7.6, -1.3)	0.01	2004-11	1118	-6.5 (-11.4, -1.4)	0.02
	2012-16	1368	9.3 (-1.1, 20.9)	0.07	2011-16	731	10.2 (-0.4, 21.9)	0.06
Non-Greek	2004-11	333	17.1 (8.1, 26.9)	0.002				
	2011-16	282	0.2 (-11.5, 13.5)	0.97				
All*	2004-08	1807	-7.5 (-14.6, 0.3)	0.06	2004-08	780	-10.7 (-19.9, -0.5)	0.04
	2008-16	3055	3.6 (0.7, 6.6)	0.02	2008-16	1327	6.1 (2.1, 10.3)	0.01

* Including missing maternal nationality values

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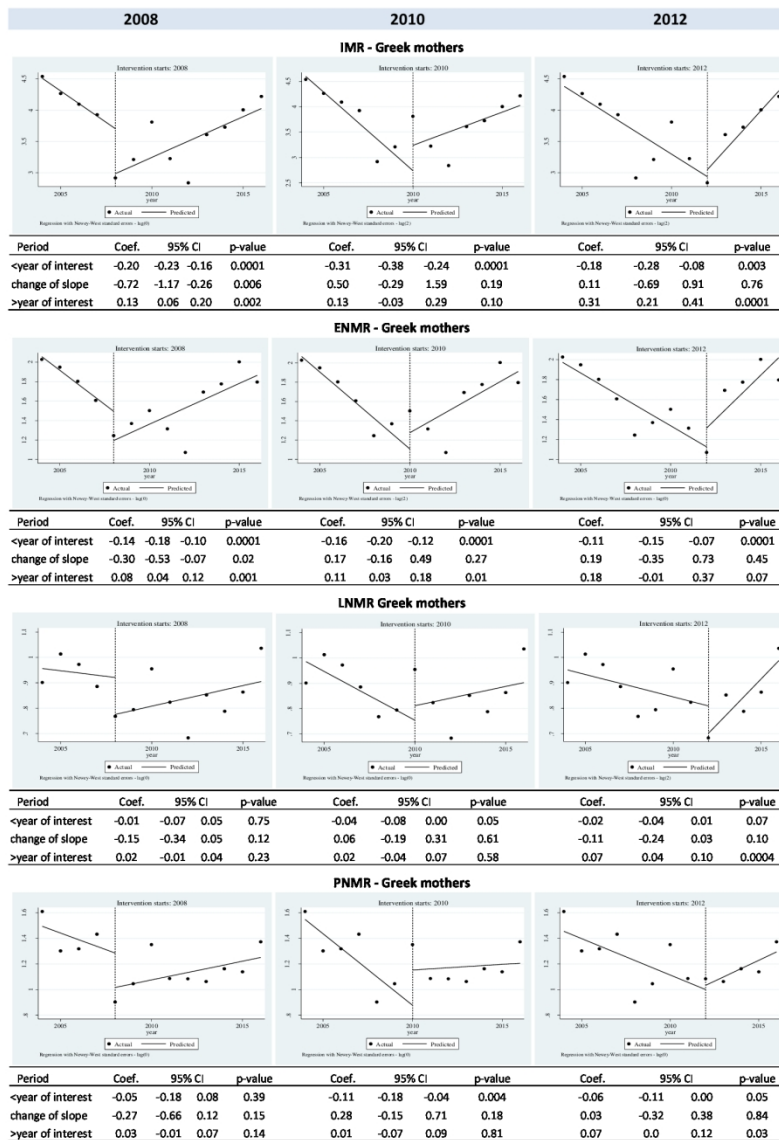
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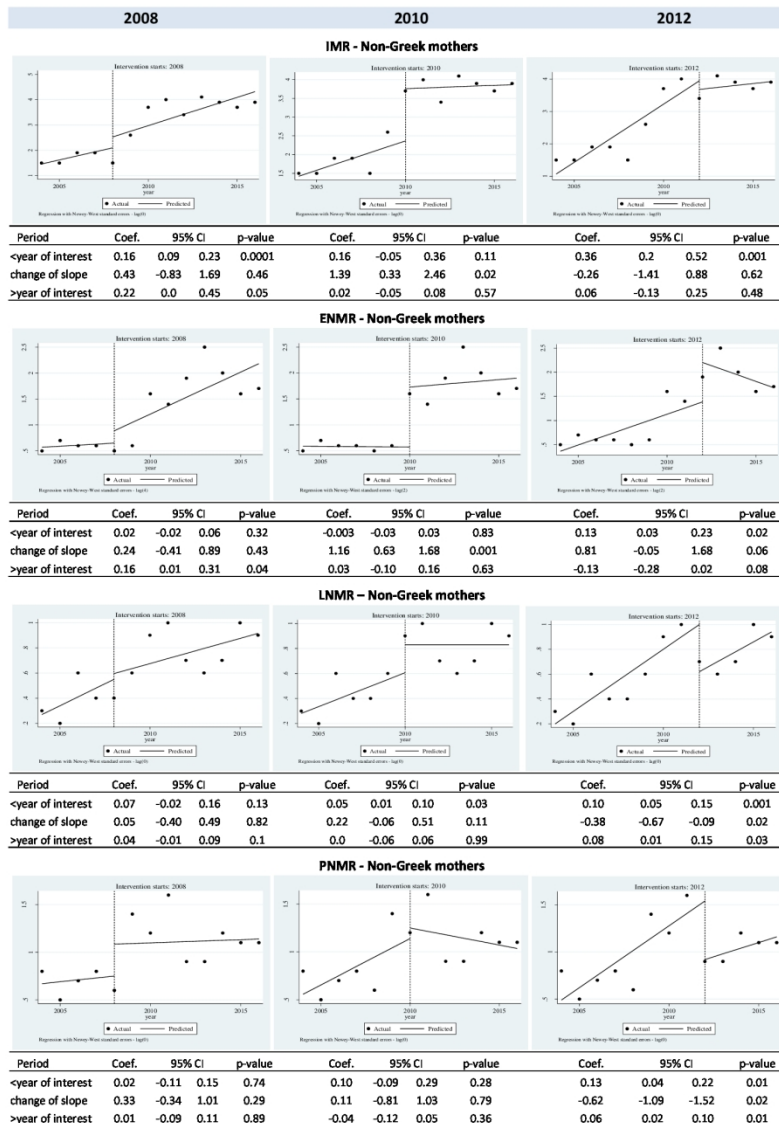
Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

60x81mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to Greek mothers.

140x198mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to non-Greek mothers.

140x198mm (300 x 300 DPI)

Research checklist- STROBE Statement—checklist

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BMJ Open

Disparities of infant and neonatal mortality trends in Greece during the years of economic crisis by ethnicity, place of residence and human development index: a nationwide population study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025287.R2
Article Type:	Research
Date Submitted by the Author:	11-Mar-2019
Complete List of Authors:	Siahanidou, Tania; First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine Dessypris, Nick; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens Analitis, Antonis; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens Mihas, Constantinos; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens Evangelou, Evangelos; Dept of Hygiene and Epidemiology; Department of Epidemiology and Biostatistics, Imperial College Chrousos, George; First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine PETRIDOU, ELENI; Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National & Kapodistrian University of Athens; Clinical Epidemiology Unit, Karolinska Institute, 171 77
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health, Health policy, Global health
Keywords:	Neonates, Mortality rates, Infant deaths, perinatal care, financial crisis

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3 **Disparities of infant and neonatal mortality trends in Greece during the years of economic**
4 **crisis by ethnicity, place of residence and human development index: a nationwide**
5 **population study**
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ABSTRACT**OBJECTIVE**

To study trends of infant (IMR) and neonatal mortality rate in Greece during the period 2004-2016 and explore the role of sociodemographic factors in the years of crisis

DESIGN

Nationwide individual data for livebirths and infant (0-11 months) deaths provided by the Hellenic Statistical Authority (ELSTAT) were examined using Poisson regression, joinpoint regression and Interrupted Time Series (ITS) statistical analyses.

SETTING

Greece

PARTICIPANTS

All infant deaths (n=4862) over the 13-year period, of which 87.2% were born to Greek mothers, and respective livebirths.

MAIN OUTCOME MEASURES

Evolution of IMR (0-364 days), early (<7 days, ENMR)/late (7-27 days, LNMR) neonatal and post neonatal (28-364 days, PNMR) mortality trends, by maternal nationality, place of residence and Human Development Index (HDI).

RESULTS

Overall, during the study-period among infants of Greek mothers, IMR -particularly PNMR- declined significantly (-0.9%; 95% CI -1.7% to -0.1% and -1.6%; -3.0% to -0.2% annually, respectively), albeit differentially by place of residence (max=IMR_{urban}: -4.1%; -5.7% to -2.5%, max=ENMR_{rural}: +24.1%; 14.2% to 34.8%). By contrast, among infants of non-Greek mothers, the low starting IMR/ENMR/LNMR/PNMR increased significantly (max ENMR: +12.5%; 8.6% to 16.5%) leading to a non-statistically significant, positive time-trend pattern overall in Greece. The inverse associations of HDI with IMR, ENMR and PNMR were restricted to Greek

1
2 mothers' infants. Of note, joinpoint regression analyses among Greek infants indicated
3
4 increases of IMR following the crisis at the limit of statistical significance (+9.3%, 2012-2016,
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6 $p=0.07$), mainly ENMR (+10.2%, 2011-2016, $p=0.06$). By contrast, the high (+17.1%; 8.1% to
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8 26.9%, $p=0.002$) IMR increases among non-Greek infants were restricted to 2004-2011 and
9
10 equalized to those of Greek mothers' infants thereafter. ITS analyses in preset years (2008,
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12 2010, 2012) overall confirmed the joinpoint results and identified adverse trends in LNMR
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14 and PNMR after 2012 among Greek infants.
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20 CONCLUSIONS

21
22 HDI and rural residence were significantly associated with IMR. The strongly decreasing IMR
23
24 -especially ENMR- trends among Greeks were stagnated after a lag time of ~four years of
25
26 crisis approximating the previously sharply increasing trends among non-Greek infants.
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35 Strengths of this study

- 36 • Longest follow-up period of national data, as contrasted to previously Greek-based
37 studies.
38
- 39 • Maternal ethnicity is for first time considered in the analyses explaining part, if not
40 most, of the heterogeneity of trends through the study period.
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- 42 • Three complimentary statistical methodologies were used to describe the overall
43 evolution of infant mortality and its components.
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52 Limitations

- 53 • Absence of a linkage system between birth and death data.
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- 55 • Data on the role of biological factors or specific causes of infant death are missing.
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7 **Abbreviations:**
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10 IM; infant mortality
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12 IMR; infant mortality rates
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14 ENMR; early neonatal mortality rates
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16 LNMR; late neonatal mortality rates
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18 PNMR; post neonatal mortality rates
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20 HDI; Human Development Index
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22 ELSTAT; Hellenic Statistical Authority
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24 ITS; Interrupted Time Series
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Introduction

Socioeconomic factors have repeatedly been recognized as strong determinants of the health status of the population, including infants.¹⁻³ Economic indicators, such as the *per capita* Gross National Product, were suggested to be at least as important contributors of infant mortality (IM) as narrowly defined factors relating to provision of medical care, e.g. the relative number of doctors or hospital beds in a community.¹ Not surprisingly, the recent economic crisis of ~2008, has been linked with declines in population and child health reflected also by increased IM rates (IMR).^{4,5} It is worth noting that in European Union countries, even a minor 1% cut in government healthcare spending was associated with significant increases in all mortality metrics, including neonatal and post neonatal IM.⁶

On the contrary, associations between the crisis and increased mortality have been questioned in other studies showing that most indicators of population health, apart from those relevant to suicides and mental health, continued improving after crisis initiation.⁷⁻¹⁰ Moreover, the economic crisis has been associated with some beneficial effects, i.e. decline in rates of road traffic accidents, and smoking cessation.^{4,9} Reasonably, the impact of the crisis on health depends on several factors including the duration and intensity of the recession, the level of health care achieved prior to the recession and the type of austerity measures applied, but also on the type of the population studied with the most vulnerable groups being disproportionately affected.^{4,11,12} Due to the latter, it was proposed that studies should focus on analyzing separately the subgroups most influenced by the crisis instead of presenting results as averages in a population.⁴

Greece has been markedly affected and still suffering the recent economic crisis. Between 2008 and 2016, the country's GDP *per capita* dropped by 26%, unemployment rate increased by more than 200% (from 7.6% to 23.3%) and the median disposable income decreased by 35%.^{13,14} The GINI index, which measures income inequality, increased by 22% and the

1
2 proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016.
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4 Total health expenditures and government expenditure on health care were both decreased
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6 by 34% per capita over the period 2008-2016,^{13,14} whereas unmet healthcare needs
7
8 increased.¹⁵ Besides, during the last years, Greece experienced large refugee flows^{16,17} with
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10 an anticipated negative impact on the country's economy and population health indicators.
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12 Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth
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14 and stillbirth rates, have been also observed;^{18,19} however, sparse data exist regarding the
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16 potential association of the crisis with IMR. It has been initially reported that during the
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18 period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period
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20 whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to
21
22 the steady decrease observed during the preceding decade.^{20,21} Ecological correlations may
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24 prone, however, to fallacies, whereas the different parts shaping the two main components
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26 of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly
27
28 examined along with other factors possibly influencing the infants' health, especially
29
30 socioeconomic status and access to health care delivery.
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32 The aims of the current study were to explore time trends in early (<7 days of life) and late
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34 (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during
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36 the period 2004-2016 after taking into account nationality and place of residence, as well as
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38 changes in the Human Development Index (HDI) during the study period as a proxy of
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40 individual and collective measures of socioeconomic impact and health care access.
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54 **Materials and Methods**

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56 Following personal contact and a signed agreement, individual data for all livebirths and
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58 infant (0-11 months) deaths were provided by the Hellenic Statistical Authority (ELSTAT) for
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60 a 13-year period (2004-2016) in two separate files: one including live births and a second

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2 one, infant deaths; linkage of the two files was not possible as the personal identification
3 number was not available in ELSTAT. Information on maternal demographic characteristics,
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5 such as nationality (available for years 2004-2016) and place of residence (available for years
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7 2004-2014), as well as on the infants' age at death, were also provided.
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11 Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late
12 neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective
13 numbers of deaths over the number of livebirths per year. Annual percent of change (APC)
14 during the study period was initially estimated through univariate Poisson regression
15 analysis using the underlying population of each set as an offset variable. Subsequently, data
16 were stratified and analyzed by maternal nationality (Greek vs. non-Greek) and place of
17 residence (Urban/Semi-urban vs. Rural). Joinpoint regression analysis²² was thereafter
18 applied to automatically derive, by a software program, different segments in the mortality
19 evolution curves overall, as well as those by maternal nationality and place of residence; the
20 Joinpoint regression analysis is usually applied to study varying trends over time in order to
21 identify the time point(s) in which the trend significantly changes. Interrupted Time Series
22 (ITS) analyses were also undertaken as a sensitivity analysis to further explore the effect of
23 crisis on IMR and its components in alternative prespecified years, notably 2008, considered
24 to indicate the initiation of the crisis in Greece -as the value of the Gross Domestic Product
25 of the country was maximum at that year but dropped afterwards (Source: Aggregate National
26 Accounts)-, and in two successive periods two years apart (2010 and 2012), to control for
27 possible time lags in observing the impact of the crisis. All ITS models were verified and
28 appropriately adjusted for possible auto-correlation; autoregressive integrated moving-
29 average models were used to control for autocorrelation and to estimate treatment effects over
30 multiple periods. In our ITS analysis a slope "<year of interest" is fitted until the introduction
31 of the crisis, ">year of interest" represents the change in the level of the mortality immediately
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2 following the initiation of the crisis and “change of slope” represents the differences between
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4 pre and post crisis intervention slopes.
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7 Human development index (HDI) is a summary measure of average achievements of a
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9 country’s population in three areas including life expectancy, education and *per capita*
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11 income indicators. Annual HDI values for the underlying populations in the year of death
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13 were extracted from the United Nations Development Program website
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15 (<http://hdr.undp.org/en/composite/HDI>), whereas Poisson regression analysis was used to
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17 explore the association of one standard deviation of HDI with total IM and its components.
18
19 All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata
20
21 software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13.
22
23 College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression
24
25 Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch,
26
27 Surveillance Research Program, National Cancer Institute).
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37 **Patient involvement**

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39 No patients were involved in setting the research question or the outcome measures, nor
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41 were they involved in developing plans for design or implementation of the study. No
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43 patients were asked to advise on interpretation or writing up of results. There are no plans
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45 to disseminate the results of the research to study participants or the relevant patient
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47 community.
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53 **Ethical approval:** Not required.
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57 **Results**

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3 The annual average number of livebirths during the study period was 105077, ranging from a
4 high 118302 (2008) to a low 91847 livebirths in 2015. The annual average proportion of
5 Greek mothers was 83.7%, whereas the remaining were mainly economic migrants. During
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7 the period 2004-2016, a total of 4862 infant deaths were recorded of whom 4238 (87.2%)
8
9 were of infants born to Greek mothers, whereas among the remaining 615 deaths of infants
10
11 born to non-Greek mothers, 298 (48.5%) were of infants born to Albanian mothers, 146
12
13 (23.7%) of infants born to mothers from Balkan countries and countries of the former Soviet
14
15 Union, 77 (12.5%) from Asia, 47 (7.6%) from countries of the European Union or other
16
17 developed countries and 47 (7.6%) from Africa. During the early and late neonatal period,
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19 2107 (43.3%) and 1136 (23.4%) deaths occurred, respectively, whereas another 1617
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21 (33.3%) of deaths were recorded in the post neonatal period. The annual average IMR was
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23 3.5 over 1000 livebirths, whereas the corresponding figures for the early, late and post
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25 neonatal period were 1.5‰, 0.8‰ and 1.2‰ respectively. The number of livebirths and
26
27 infant deaths, total IMR per 1000 livebirths in infants born to Greek and non-Greek mothers,
28
29 as well as HDI values, in Greece, during the study period, are shown in Table 1. Moreover,
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31 infant deaths and total infant mortality rates (IMR) by place of residence (Urban/Semi-urban
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33 vs. Rural) are shown in Suppl. Table 1.

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44 Of note, in the beginning of the study period in 2004, notably well before the initiation of
45
46 the crisis, IMR and its components were 2- to 4-fold higher among infants born to Greek
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48 mothers in comparison with rates in infants born to non-Greek origin mothers. During the
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50 subsequent 4-5 years, however, rates among Greeks followed downward trends whereas
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52 among non-Greeks inflated reaching almost similar values to those observed in infants born
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54 to Greek mothers (Figure 1).

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59 Overall, during the study-period, among infants born to Greek mothers, IMR, particularly
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PNMR, declined significantly (-0.9%; 95% CI -1.7% to -0.1% and -1.6%; -3.0% to -0.2%

1
2 annually, respectively, $p=0.02$ for each), albeit differentially by place of residence (Table 2);
3
4 significant decline of IMR trends (-3.5%; -4.6% to -2.4% annually, $p<0.0001$) and all its
5
6 components was observed among infants born to Greek mothers living in urban areas
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8 whereas, among infants born to Greek mothers in rural areas, a significant increase of IMR
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10 trend was observed (+5.2%; 1.3% to 9.3% annually, $p=0.01$) resulting mainly from increased
11
12 ENMR (+24.1%; 14.2% to 34.8% annually, $p<0.0001$). By contrast, among infants of non-
13
14 Greek mothers, the low starting IMR increased significantly (+9.4%; 6.9% to 11.9% annually,
15
16 $p<0.0001$), due to significant increases of ENMR, LNMR and PNMR (max ENMR: +12.5%;
17
18 8.6% to 16.5% annually, $p<0.0001$) leading to a non-significant pattern of IMR evolution for
19
20 Greece overall ($p=0.50$) (Table 2). Further analysis by nationality of non-Greek mothers
21
22 showed significant increases of IMR trends in all ethnic groups with average annual percent
23
24 change 7.6% (95% CI; 4.2% to 11.1%) in infants born to Albanian mothers, 8.6% (3.7% to
25
26 13.8%) in infants born to mothers from Balkan countries and countries of the former Soviet
27
28 Union, 9.4% (2.8% to 16.3%) in infants born to mothers from Asia, 9.4% (1.1% to 18.3%) in
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30 infants born to mothers from countries of the European Union or other developed countries,
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32 and 21.1% (11.0% to 32.3%) in infants born to mothers from Africa. HDI trends increased
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34 significantly, by 0.1% (95% CI 0.06% to 0.13%) annually during the study period. Inverse
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36 associations of HDI with IMR, ENMR and PNMR, restricted to Greek mothers' infants, were
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38 observed (Table 2).
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49 In order to examine whether IMR, in our study population, might have influenced by any
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51 variation in the registration of births in cases of uncertain viability, we analyzed separately
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53 the infant deaths in the first day of life; trends of IMR in this age group, over the study
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55 period, were non-significant (average annual percent change: -1.22%; 95% CI: -3.79% to
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57 1.42%; $p=0.36$).
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Results of joinpoint regression analyses were similar to those derived by the Poisson regression apart from models displayed in Table 3 pertaining to IMR and ENMR trends. Specifically, a break was identified among Greek infants restricting the decreasing IMR trend to the period 2004-2012 (-4.5%; 95% CI -7.6% to -1.3% annually, $p=0.01$); this was mainly due to a significant decline in ENMR trend till 2011 (-6.5%; 95% CI -11.4% to -1.4% annually, $p=0.02$). Of note, however, in the most recent study period (2012-2016) increases of IMR at the limit of statistical significance (+9.3% annually, $p=0.07$) and ENMR (+10.2% annually, $p=0.06$) were observed with no indication any more of differentiation by place of residence. By contrast, among infants born to non-Greek mothers, the high IMR increases (+17.1%; 95% CI 8.1% to 26.9% annually, $p=0.002$) were restricted to the period 2004-2011 with no fluctuation thereafter; finally, IMR approximated those of Greek mothers' infants (Table 3). ITS analyses in the preset years 2008, 2010 and 2012 (Figures 2 and 3) confirmed the joinpoint analysis results and further identified adverse trends in LNMR and PNMR after 2012 among Greek infants (Figure 2).

Discussion

Trends of neonatal and infant mortality in Greece, spanning from year 2004 -before the initiation of crisis in 2008- to year 2016, are not homogeneous, given significant increases in the relatively small proportion of infants born to non-Greek nationality mothers as contrasted to declining IMR trends among Greek infants, and increases in indices indicating differentials in proxies of health care access among Greek neonates, such as ENMR, noted ~four years after the crisis, which led to offsets of the urbanization differentials observed overall. Specifically, the "brake" of 2012 identified increases of ~10% annually, thereafter (at the limit of statistical significance), in IMR and ENMR trends among infants born to Greek mothers. Changes in HDI during the study period were also reflected in the inverse

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2 associations of HDI with ENMR and IMR, but also PNMR, among infants born to Greek
3 mothers.
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7 Strengths of the present investigation, as contrasted to previously Greek-based published
8 studies,^{9,18,20,21,23} include the longest follow-up period of national data, namely since 2004,
9 before the crisis, when the first data on maternal ethnicity became electronically available,
10 to the latest available year 2016. Of great importance is also the fact that, for the first time,
11 the maternal ethnicity was considered in the analyses explaining part, if not most, of the
12 heterogeneity of trends through the study period. To this end, three complimentary
13 statistical methodologies were used to describe the overall evolution depicted in Figure 1.
14 Thus, we were able to enhance the validity of the results pertaining to the study of the
15 evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association
16 with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which
17 individual data have been available on a nationwide level among both deaths and livebirths
18 during the study period. Calculation of IMR and its components was based on the number of
19 livebirths; yet, the absence of a linkage system between birth and death data, as well as
20 other official registries in Greece, has not allowed use of known determinants of
21 socioeconomic deprivation or social coherence, such as parental education,
22 employment/occupation, marital status, family income and household size. Neither were
23 data on the role of biological factors, such as parental age, gestational age and birthweight,
24 or multiplicity of pregnancy available for both the livebirths and deaths series.^{5,19,24} Besides,
25 the study period, with available information on maternal nationality and place of residence,
26 was rather short leading to ITS analyses with few data points; however, ITS analysis can be
27 used even for few observations; no log-transformation is needed but the results should be
28 interpreted with caution as the power depends on various factors.²⁵ Lastly, analyses by specific
29 cause of infant death were not set among the outcome measures of this study.
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3 Assessing migration as a determinant of perinatal health outcome and infant death in the
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5 developed countries is a complex undertaking resulting in conflicting results of published
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7 studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor
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9 for unfavorable perinatal outcomes and increased neonatal and infant mortality,^{18,26-33}
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11 especially if it coincides with a financial crisis, as was the case in Greece. Factors possibly
12
13 contributing to the increased risk for poorer outcomes among children born to migrants
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15 include socioeconomic disadvantage, poor communication, discrimination, reduced
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17 utilization of health facilities, low quality of care, but also stress and consanguinity or
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19 differing attitudes to screening and termination of pregnancy associated with preterm birth,
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21 low birth weight or congenital anomalies and lethal inherited diseases.^{26,30,34-36} By contrast,
22
23 other studies present similar or even better perinatal health outcomes among some migrant
24
25 groups than among natives (“healthy migrant effect/paradox”).^{26-28,37,38} Refugees have been
26
27 recognized as the most vulnerable group suffering increased severe neonatal morbidity and
28
29 infant mortality risk,^{26,28} although no absolutely clear pattern regarding refugee or non-
30
31 refugee status among migrants has been identified.³⁴
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34 In our study, starting rates of IMR and its components among infants born to non-Greek
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36 mothers were lower compared to those of Greek mothers. Of note, the ratio of non-Greek
37
38 infants among live births during 2009-2016 vs. 2004-2008 was only 1.32, whereas the
39
40 respective figure among infant deaths was almost 3-fold (data not shown). Actually, in the
41
42 pre-crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most
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44 of them of Albanian nationality living for many years, or even born, in Greece. After 2008,
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46 Greece experienced an influx of refugees with the majority of them fleeing from war and
47
48 terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other
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50 countries.^{16,17} It could be suggested that changes in the homogeneity of foreign mothers
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52 during the study period, in association with the country’s economic difficulties, might have
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2 led from the “healthy migrant effect”, observed before 2008, to the deterioration of IM
3 indicators and IMR trends, afterwards, in infants born to non-Greek mothers. We did
4 observe significant increases in IMR trends in all ethnic groups of non-Greek mothers during
5 the study period, especially in infants born to mothers from Africa; however as the numbers
6 by individual maternal nationality were rather small, this issue needs to be further studied.
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10 Simultaneously with immigration to/through Greece, the country experienced the third
11 wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left
12 Greece since the onset of the economic crisis, in 2008, seeking new opportunities and
13 employment in other countries, mainly Germany, the United Kingdom and the
14 Netherlands.^{39,40} The current emigration wave of Greeks involved mostly highly-educated
15 people (the so called “brain-drain”) of young age, leading to a decrease in the number of
16 Greek women of childbearing age.⁴¹ This fact, along with the decrease in the fertility rate by
17 almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual
18 number of livebirths in Greece by almost 23% during the period of the economic crisis.^{41,42}
19 Furthermore, the flow of mostly affluent and well educated people going outside Greece
20 could also contribute to increases in IMR among Greek children following the crisis.
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42 Indeed, the strongly decreasing IMR, especially ENMR, trends among Greek infants were
43 stagnated after a lag time of ~four years of crisis and equalized with the previously sharply
44 increasing trends among non-Greek maternal nationality infants; this time lag is reasonable⁴³
45 and in line with previous findings showing that following reductions in the government
46 healthcare spending in Europe, the greatest negative effect on neonatal and post neonatal
47 mortality was 4 and 5 years later, respectively.⁶ The irony is that the period 2012-2016,
48 during which the crisis was deepening^{13,14} and stricter economic austerity measures were
49 applied,⁴⁴ disparities gap in IMR trends diminished against the Greek population; IMR trends
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3 deteriorated only in infants born to Greek mothers, whereas in infants born to non-Greek
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5 mothers IMR trends approached an anelastic highest value up to 2011 with no fluctuation
6
7 thereafter. The importance of two sub-analyses of IMR trends by maternal nationality (Greek
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9 vs. non-Greek) should be emphasized; when trends in the entire study population were
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11 assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a
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13 break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of
14
15 previous relevant studies in Greece which did not take into consideration the maternal
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17 nationality.²⁰

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19 Disparities in IMR still exist across geographic areas even in well developed countries; i.e.
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21 IMR in the United States vary by urbanization level of maternal residency being lowest in
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23 large urban counties but highest in rural areas.⁴⁵ Rural women may face health challenges
24
25 related to geographic barriers to care (less timely and/or appropriate care) and physician
26
27 shortages, but they may also present differences in a number of socioeconomic and
28
29 demographic risk factors, such as less education, lower income, younger age at pregnancy,
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31 or greater number of children, in comparison with their urban counterparts.^{46,47} The
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33 increasing IMR trends during the study period in infants born to Greek mothers living in rural
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35 areas, as opposed to the declining IMR trends in those born to Greek mothers living in
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37 urban/semi urban areas, is worrisome; specific causes should be further studied and
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39 addressed. As regards infants born to non-Greek mothers, the increasing IMR trends despite
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41 living in urban areas can be explained by previous reports showing that other risk factors, i.e.
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43 young maternal age (<20 years) or maternal ethnic minority, may be more powerful than
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45 place of residence.⁴⁷

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47 As expected, among the three IMR components, ENMR was the most “sensitive” in reflecting
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49 adverse impacts on child health as further reflected in the IMR trends. Specifically, ENMR
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51 was overall positively associated with rural place of residence of Greek children, notably
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2 before the “break” of 2012, with the increased ENMR neutralizing the urbanization
3 differentials among newborns of Greek mothers. ENMR, in developed countries, including
4 Greece, represents more than 70% of neonatal deaths on account mainly of prematurity/low
5 birth weight and congenital anomalies.^{14,48-51} Actually, it reflects perinatal health and care
6 during pregnancy and labor, and also postnatal care in the first week of life.⁵⁰ Increased
7 incidence of impaired perinatal parameters including low birth weight, prematurity, and
8 increased maternal age and rate of caesarian section, have been reported during the years
9 of the economic decline in Greece.^{18,19} Cuts in public health expenditures between 2008 and
10 2016, reduction in health care workforce and pediatric nurses, as well as reduction in the
11 number of obstetrics beds, obstetricians and midwives (-45.5%, -60.2% and -27.5%,
12 respectively)¹⁴ could possibly explain, at least in part, the observed positive ENMR trends
13 during the post-crisis period in Greece.

14
15 The exact mechanisms leading to the disparities in trends of neonatal and infant mortality
16 observed in this study remain to be further explored. Specific maternal, family and infant
17 features, including detailed and punctual information on the causes of infant deaths, would
18 have shed more light on the links between IMR trends and socioeconomic factors but were
19 beyond the scope of this article and left for future research. Meanwhile, policies and
20 programs should be implemented to mitigate the negative impact of the crisis on population
21 and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of
22 low income, or rural place of residence, should be specifically addressed and their rights to
23 health protected. Barriers in the access of refugees to the Greek health care system have
24 been identified; they are mostly related to language, culture, and inadequate information
25 about the healthcare system, but also include difficulties in the coordination of Health
26 Services, transportation problems, issues in obtaining expertise medical assessment in the
27 camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for

1
2 health and social care services, and administrative barriers, among others.⁵² In response, the
3
4 Greek government and several Non-Governmental Organizations initiated commendable
5
6 actions, i.e. National Health System services free of charge for uninsured and vulnerable
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8 social groups including asylum seekers , translation services in public hospitals, access to
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10 specialist care/treatment with Gynecologists (mostly women), midwives, dentists,
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12 psychologists, and psychiatrists being lately included in the camp clinics;⁵² these actions may
13
14 have prevented deterioration of IMR which are being kept at steady levels after 2011 in
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16 infants of non-Greek mothers; efforts should be continued and intensified, however, as to
17
18 ensure equity with local populations. Strong governmental integration policy for minorities
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20 paired with initiatives to improve social coherence, a deeply rooted mechanism for
21
22 protection of health among those in need in the Greek society, along with further
23
24 improvements in primary health care delivery could help to alleviate the cost in infant lives
25
26 and ensure healthy adulthood.^{32,51} Irrespective of the crisis, improvements in the quality of
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28 perinatal and neonatal care, including centralization of very preterm deliveries,
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30 establishment of regional perinatal centers, monitoring of the implementation of evidence-
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32 based practices in maternity and neonatal units, as well as increase in health expenditures,
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34 health care workforce, number of doctors and midwives/nurses, could decrease ENMR,
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36 eventually leading to overall decrease in IMR in Greece.⁵⁰
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51 REFERENCES

52
53 1. Petridou E, Valadian I, Trichopoulos D, Tzonou A, Kyriopoulos Y, Matsaniotis N. Medical
54
55 services and socioeconomic factors: Determinants of infant mortality in Greece. *Hygie*
56
57 1989;3:20-3.
58
59
60

- 1
2
3 2. WHO. The determinants of health. <http://www.who.int/hia/evidence/doh/en> (Date of
4
5 access: 30/5/2018)
- 6
7 3. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England
8
9 compared with Sweden: a birthcohort study. *Lancet* 2018;391(10134):2008-2018.
10
11 doi:10.1016/S0140-6736(18)30670-6.
- 12
13 4. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al; International Network for
14
15 Research in Inequalities in Child Health (INRICH). Impact of the 2008 economic and financial
16
17 crisis on child health: a systematic review. *Int J Environ Res Public Health* 2014;11:6528-46.
18
19 doi:10.3390/ijerph110606528.
- 20
21 5. Glonti K, Gordeev VS, Goryakin Y, Reeves A, Stuckler D, McKee M, Roberts B. A systematic
22
23 review on health resilience to economic crises. *PLoS One* 2015;10:e0123117.
24
25 doi:10.1371/journal.pone.0123117.
- 26
27 6. Budhdeo S, Watkins J, Atun R, Williams C, Zeltner T, Maruthappu M. Changes in
28
29 government spending on healthcare and population mortality in the European union, 1995–
30
31 2010: a cross-sectional ecological study. *J R Soc Med* 2015;108:490-8.
32
33 doi:10.1177/0141076815600907.
- 34
35 7. Tapia Granados JA, Rodriguez JM. Health, economic crisis, and austerity: A comparison of
36
37 Greece, Finland and Iceland. *Health Policy* 2015;119:941-53.
38
39 doi:10.1016/j.healthpol.2015.04.009.
- 40
41 8. Regidor E, Barrio G, Bravo MJ, de la Fuente L. Has health in Spain been declining since the
42
43 economic crisis? *J Epidemiol Community Health* 2014;68:280-2. doi:10.1136/jech-2013-
44
45 202944.
- 46
47 9. Laliotis I, Ioannidis JPA, Stavropoulou C. Total and cause-specific mortality before and
48
49 after the onset of the Greek economic crisis: an interrupted time-series analysis. *Lancet*
50
51
52
53
54
55
56
57
58
59
60 *Public Health* 2016;1: e56–e65. doi:10.1016/S2468-2667(16)30018-4.

10. Parmar D, Stavropoulou C, Ioannidis JP. Health outcomes during the 2008 financial crisis in Europe: systematic literature review. *BMJ* 2016;354:i4588. doi:10.1136/bmj.i4588.
11. O'Donnell C, Burns N, Dowrick C, Lionis C, MacFarlane A; RESTORE team. Health-care access for migrants in Europe. *Lancet* 2013; 382:393. doi: 10.1016/S0140-6736(13)61666-9.
12. Karanikolos M, Heino P, McKee M, Stuckler D, Legido-Quigley H. Effects of the Global Financial Crisis on Health in High-Income OECD Countries: A Narrative Review. *Int J Health Serv* 2016;46:208-40. doi: 10.1177/0020731416637160.
13. Organisation for Economic Co-operation and Development OECD data. <https://data.oecd.org> (Date of access: 30/5/2018) (2016).
14. Hellenic Statistical Authority *Statistics*. www.statistics.gr (Date of access: 30/5/2018) (2016).
15. Zavras D, Zavras AI, Kyriopoulos II, Kyriopoulos J. Economic crisis, austerity and unmet healthcare needs: the case of Greece. *BMC Health Serv Res* 2016;16:309. doi:10.1186/s12913-016-1557-5.
16. European Union. The EU and the migration crisis, July 2017, <http://publications.europa.eu>
17. Mertens E, Rockenschaub G, Economopoulou A, Kreidl P. Assessment of public health issues of migrants at the Greek-Turkish border, April 2011. *Euro Surveill* 2012 Jan 12;17(2). pii: 20056.
18. Zografaki I, Papamichail D, Panagiotopoulos T. Adverse effect of the financial crisis in Greece on perinatal factors. *Eur J Public Health* 2018 [Epub ahead of print]. doi: 10.1093/eurpub/cky078.
19. Sdoná E, Papamichail D, Ragkou E, Briana DD, Malamitsi-Puchner A, Panagiotopoulos T. Greek economic crisis and impaired perinatal parameters: experience from a public

- 1
2
3 maternity hospital. *J Matern Fetal Neonatal Med* 2018;31:2371-5.
4
5 doi:10.1080/14767058.2017.1342803.
6
7 20. Michas G, Varytimiadi A, Chasiotis I, Micha R. Maternal and child mortality in Greece.
8
9 *Lancet* 2014;383:691-2. doi:10.1016/S0140-6736(14)60251-8.
10
11
12 21. Filippidis F, Gerovasili V, Millett C, Tountas Y. Medium-term impact of the economic crisis
13
14 on mortality, health-related behaviours and access to healthcare in Greece. *Sci Rep*
15
16 2017;7:46423. doi:10.1038/srep46423.
17
18
19 22. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
20
21 applications to cancer rates. *Stat Med* 2000;19:335-51. PMID:10649300
22
23
24 23. Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in
25
26 Greece in the literature from 2009 to 2013: a systematic review. *Health Policy* 2014;115:111-
27
28 9. doi: 10.1016/j.healthpol.2014.02.002.
29
30
31 24. Petridou ET, Georgakis MK, Erdmann F, et al. Advanced parental age as risk factor for
32
33 childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia
34
35 International Consortium. *Eur J Epidemiol* 2018. doi:10.1007/s10654-018-0402-z. [Epub
36
37 ahead of print].
38
39
40 25. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation
41
42 of public health interventions: a tutorial. *Int J Epidemiol* 2017;46(1):348-55. doi:
43
44 10.1093/ije/dyw098.
45
46
47 26. Gissler M, Alexander S, MacFarlane A, et al. Stillbirths and infant deaths among migrants
48
49 in industrialized countries. *Acta Obstet Gynecol Scand* 2009;88:134-48.
50
51
52 doi:10.1080/00016340802603805.
53
54
55 27. Gagnon AJ, Zimbeck M, Zeitlin J, et al. Migration to western industrialized countries and
56
57 perinatal health: a systematic review. *Soc Sci Med* 2009;69:934-46.
58
59
60 doi:10.1016/j.socscimed.2009.06.027.

- 1
2
3 28. Wanigaratne S, Cole DC, Bassil K, et al. Severe Neonatal Morbidity Among Births to
4
5 Refugee Women. *Matern Child Health J* 2016;20:2189-98. doi:10.1007/s10995-016-2047-4.
6
7
8 29. Puthussery S. Perinatal outcomes among migrant mothers in the United Kingdom: Is it a
9
10 matter of biology, behaviour, policy, social determinants or access to health care? *Best Pract*
11
12 *Res Clin Obstet Gynaecol* 2016;32:39-49. doi:10.1016/j.bpobgyn.2015.09.003.
13
14
15 30. Wanner P, Bollini P. The contribution of the foreign population to the high level of infant
16
17 mortality in Switzerland: a demographic analysis. *BMC Pregnancy Childbirth* 2017;17:151.
18
19 doi:10.1186/s12884-017-1332-6.
20
21
22 31. Cantarutti A, Franchi M, Monzio Compagnoni M, Merlino L, Corrao G. Mother's
23
24 education and the risk of several neonatal outcomes: an evidence from an Italian
25
26 population-based study. *BMC Pregnancy Childbirth* 2017;17:221. doi:10.1186/s12884-017-
27
28 1418-1.
29
30
31 32. Bollini P, Pampallona S, Wanner P, Kupelnick B. Pregnancy outcome of migrant women
32
33 and integration policy: a systematic review of the international literature. *Soc Sci Med*
34
35 2009;68:452-61. doi:10.1016/j.socscimed.2008.10.018.
36
37
38 33. Gotsens M, Malmusi D, Villarroel N, et al. Health inequality between immigrants and
39
40 natives in Spain: the loss of the healthy immigrant effect in times of economic crisis. *Eur J*
41
42 *Public Health* 2015;25:923-9. doi:10.1093/eurpub/ckv126.
43
44
45 34. Nybo Andersen AM, Gundlund A, Villadsen SF. Stillbirth and congenital anomalies in
46
47 migrants in Europe. *Best Pract Res Clin Obstet Gynaecol* 2016;32:50-9.
48
49 doi:10.1016/j.bpobgyn.2015.09.004.
50
51
52 35. Di Renzo GC, Tosto V, Giardina I. The biological basis and prevention of preterm birth.
53
54 *Best Pract Res Clin Obstet Gynaecol* 2018. doi:10.1016/j.bpobgyn.2018.01.022. [Epub ahead
55
56 of print].
57
58
59
60

- 1
2
3 36. Wanigaratne S, Cole DC, Bassil K, Hyman I, Moineddin R, Urquia ML. The influence of
4
5 refugee status and secondary migration on preterm birth. *J Epidemiol Community Health*
6
7 2016;70:622-8. doi:10.1136/jech-2015-206529.
8
9
10 37. Kirby RS. Perinatal outcomes and nativity: does place of birth really influence infant
11
12 health? *Birth* 2011;38:354-6. doi:10.1111/j.1523-536X.2011.00505.x.
13
14
15 38. Sdoná E, Papamichail D, Ragkou E, et al. Migration status and perinatal parameters in a
16
17 Greek public maternity hospital: an illustration of the "healthy immigrant effect". *J Matern*
18
19 *Fetal Neonatal Med* 2017. doi: 10.1080/14767058.2017.1371131. [Epub ahead of print].
20
21
22 39. Eurostat, "Emigration by age group, sex and citizenship".
23
24 http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=migr_emi1ctz&lang=en (last
25
26 updated: 04/04/2018).
27
28
29 40. Cavounidis J. The changing face of emigration: Harnessing the potential of the New
30
31 Greek Diaspora. Washington, DC: Migration Policy Institute, 2015.
32
33
34 41. Vrachnis N, Vlachadis N, Iliodromiti Z, Vlachadi M, Creatsas G. Greece's birth rates and
35
36 the economic crisis. *Lancet* 2014;383:692-3. doi: 10.1016/S0140-6736(14)60252-X.
37
38
39 42. Eurostat, "Fertility indicators". [http://appsso.eurostat.ec.europa.eu/nui/show.](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en)
40
41 [do?dataset=demo_find&lang=en](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en) (last updated: 20/09/2018)
42
43
44 43. Karanikolos M, Mladovsky P, Cylus J, et al. Financial crisis, austerity, and health in
45
46 Europe. *Lancet* 2013;381:1323-31. doi:10.1016/S0140-6736(13)60102-6.
47
48
49 44. Burki T. Health under austerity in Greece. *Lancet* 2018;391:525-6. doi:10.1016/S0140-
50
51 6736(18)30242-3.
52
53
54 45. Ely DM, Driscoll AK, Mathews TJ. Infant mortality rates in rural and urban areas in the
55
56 United States, 2014. *NCHS data brief*, No 285. Hyattsville, MD: National Center for Health
57
58 Statistics, 2017.
59
60

- 1
2
3 46. Van de Poel E, O'Donnell O, Van Doorslaer E. What explains the rural-urban gap in infant
4 mortality: household or community characteristics? *Demography* 2009;46:827-50.
5
6 doi:org/10.1353/dem.0.0074.
7
8
9
10 47. Harris DE, Aboueissa AM, Baugh N, Sarton C. Impact of rurality on maternal and infant
11 health indicators and outcomes in Maine. *Rural Remote Health* 2015;15:3278.
12
13
14 48. Heron M. Deaths: Leading Causes for 2015. *Natl Vital Stat Rep* 2017;66:1-76.
15
16
17 49. Roncancio CP, Misnaza SP, Peña IC, Prieto FE, Cannon MJ, Valencia D. Trends and
18 characteristics of fetal and neonatal mortality due to congenital anomalies, Colombia 1999-
19 2008. *J Matern Fetal Neonatal Med* 2018;31:1748-55. doi:10.1080/14767058.2017.1326901.
20
21
22
23 50. Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: A challenge
24 worldwide. *Semin Fetal Neonatal Med* 2017;22:153-60. doi:10.1016/j.siny.2017.02.006.
25
26
27
28 51. Alexander M, Harding M, Lamarche C. Quantifying the impact of economic crises on
29 infant mortality in advanced economies. *Applied Economics* 2011; 43: 3313–23.
30
31
32
33
34
35
36
37 52. Kotsiou OS, Kotsios P, Srivastava DS, Kotsios V, Gourgoulisanis KI, Exadaktylos AK. Impact
38 of the Refugee Crisis on the Greek Healthcare System: A Long Road to Ithaca. *Int J Environ*
39
40
41
42
43
44
45
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Contributors: EP and GC were involved in the initial conception of the study. All authors contributed to the design, analysis and interpretation of data. TS, ND and EP developed the first draft of the manuscript and all authors critically revised it and approved the final version. ND, AA and CM performed the statistical analyses; EE reviewed statistics and contributed significantly for ITS analyses. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the

1
2 work are appropriately investigated and resolved. The corresponding author ensures that all
3
4 the journal's administrative requirements are properly completed.
5
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9

10 **Acknowledgements:** ELSTAT has provided individual anonymized data.
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14

15 **Data sharing:** Data are available upon request from ELSTAT
16
17

18 (<http://www.statistics.gr/el/statistical-data-request>)
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23 **Funding Statement**

24
25 This research received no specific grant from any funding agency in the public, commercial
26
27 or not-for-profit sectors'
28
29
30
31

32 **Competing interests statement**

33
34 All authors have completed the ICMJE uniform disclosure form at
35
36 www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the
37
38 submitted work; no financial relationships with any organizations that might have an interest
39
40 in the submitted work in the previous three years; no other relationships or activities that
41
42 could appear to have influenced the submitted work.
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Figure Legends

Figure 1. Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

Figure 2. Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to Greek mothers.

Figure 3. Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to non-Greek mothers.

Table 1. Livebirths, infant deaths, total infant mortality rates (IMR) per 1000 livebirths in infants born to Greek and non-Greek mothers, and Human Development Index (HDI), in Greece during the period 2004-2016.

Year	Infants born to Greek mothers			Infants born to non-Greek mothers			HDI
	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths	
2004	88805	403	4.5	16825	26	1.5	0.835
2005	89819	383	4.3	17678	26	1.5	0.845
2006	92590	379	4.1	19396	36	1.9	0.851
2007	91462	359	3.9	20412	38	1.9	0.849
2008	96329	281	2.9	21931	32	1.5	0.857
2009	95640	307	3.2	22244	58	2.6	0.858
2010	93209	355	3.8	21351	80	3.7	0.856
2011	87445	282	3.2	18680	74	4.0	0.852
2012	84868	241	2.8	15153	52	3.4	0.854
2013	80938	292	3.6	13063	53	4.1	0.856
2014	79985	298	3.7	12144	47	3.9	0.864
2015	79919	320	4.0	11919	44	3.7	0.866
2016	80166	338	4.2	12721	49	3.9	0.868

*excluding missing maternal nationality values

Table 2. Poisson regression derived changes and 95% Confidence Intervals (CI) of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in time periods with available data: Annual Percent of Change (APC) for place of residence (2004-2014) and maternal nationality (2004-2016); Percept of Change (PC) for 1 Standard Deviation of Human Development Index (HDI, 2004-2016) controlling for year of birth.

Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	-0.9 (-1.7, -0.1)	0.02	1849	-0.6 (-1.8, 0.7)	0.35	995	-0.6 (-2.3, 1.1)	0.46	1393	-1.6 (-3.0, -0.2)	0.02
Non-Greek	615	9.4 (6.9, 11.9)	<.0001	258	12.5 (8.6, 16.5)	<.0001	138	8.0 (3.1, 13.2)	0.001	218	4.4 (0.6, 8.4)	0.02
All*	4862	0.3 (-0.5, 1.0)	0.50	2107	0.9 (-0.3, 2.1)	0.13	1136	0.4 (-1.2, 2.0)	0.65	1617	-0.9 (-2.2, 0.5)	0.20
Urbanization												
Urban-Semi urban												
Greek	3305	-3.5 (-4.6, -2.4)	<.0001	1476	-4.1 (-5.7, -2.5)	<.0001	781	-2.7 (-4.9, -0.5)	0.02	1048	-3.3 (-5.2, -1.4)	0.001
Non-Greek	494	13.3 (9.9, 16.9)	<.0001	208	19.4 (13.7, 25.3)	<.0001	110	11.2 (4.2, 18.6)	0.001	176	8.2 (2.8, 13.8)	0.002
Any*	3807	-1.6 (-2.6, -0.6)	0.002	1684	-1.7 (-3.2, -0.1)	0.03	894	-1.2 (-3.3, 0.9)	0.27	1229	-1.8 (-3.6, 0.0)	0.05
Rural												
Greek	275	5.2 (1.3, 9.3)	0.01	69	24.1 (14.2, 34.8)	<.0001	62	4.6 (-3.4, 13.3)	0.27	144	-2.0 (-7.1, 3.3)	0.44
Non-Greek	22	-6.9 (-19.4, 7.5)	0.33	7	14.8 (-8.0, 43.3)	0.22	3	-1.9 (-34.7, 47.4)	0.93	12	-12.4 (-32.0, 12.9)	0.31
All*	298	4.3 (0.6, 8.2)	0.02	76	24.4 (14.8, 34.7)	<.0001	65	3.6 (-4.2, 12.1)	0.38	157	-3.4 (-8.2, 1.6)	0.18
HDI												
PC			PC			PC			PC			
Greek		-8.6 (-14.8, -1.9)	0.01		-11.3 (-20.8, -1.4)	0.03		3.5 (-10.9, 20.1)	0.66		-12.3 (-22.2, -1.2)	0.03
Non-Greek		-5.7 (-25.0, 18.7)	0.62		-19.8 (-44.8, 16.6)	0.25		20.0 (-28.6, 101.7)	0.49		-1.3 (-30.7, 40.5)	0.94
All*		-9.5 (15.3, -3.2)	0.004		-14.0 (-22.3, -4.7)	0.004		3.3 (-10.4, 19.3)	0.65		-11.4 (-20.8, -0.7)	0.04

*including missing maternal nationality values

Table 3. Joinpoint regression derived Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant (IMR) and early neonatal mortality rates (ENMR) by maternal nationality (only for indices showing breaks in the time period examined).

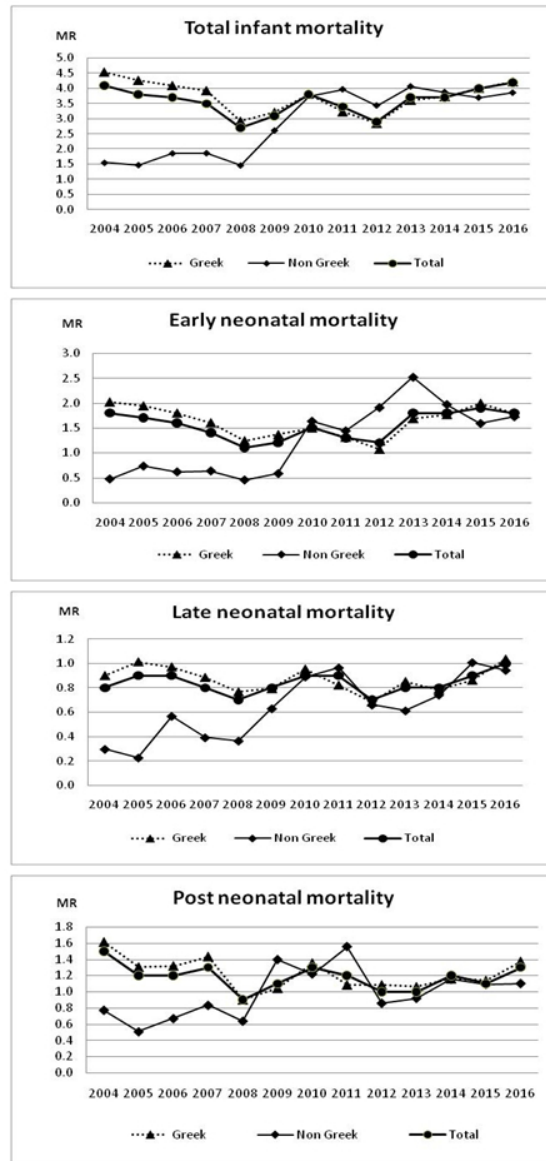
Variable	Years	N	IMR APC (95% CI)	p-value	Time period	N	ENMR APC (95% CI)	p-value
Greek	2004-12	2870	-4.5 (-7.6, -1.3)	0.01	2004-11	1118	-6.5 (-11.4, -1.4)	0.02
	2012-16	1368	9.3 (-1.1, 20.9)	0.07	2011-16	731	10.2 (-0.4, 21.9)	0.06
Non-Greek	2004-11	333	17.1 (8.1, 26.9)	0.002				
	2011-16	282	0.2 (-11.5, 13.5)	0.97				
All*	2004-08	1807	-7.5 (-14.6, 0.3)	0.06	2004-08	780	-10.7 (-19.9, -0.5)	0.04
	2008-16	3055	3.6 (0.7, 6.6)	0.02	2008-16	1327	6.1 (2.1, 10.3)	0.01

* Including missing maternal nationality values

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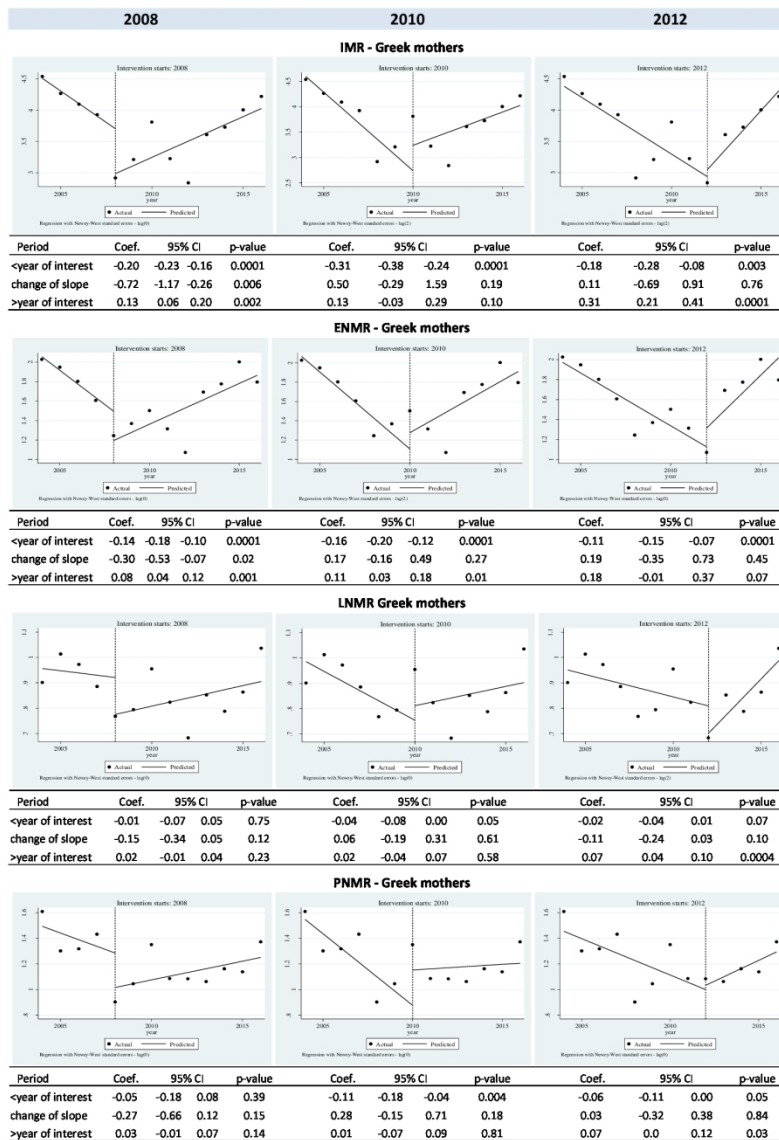
For peer review only

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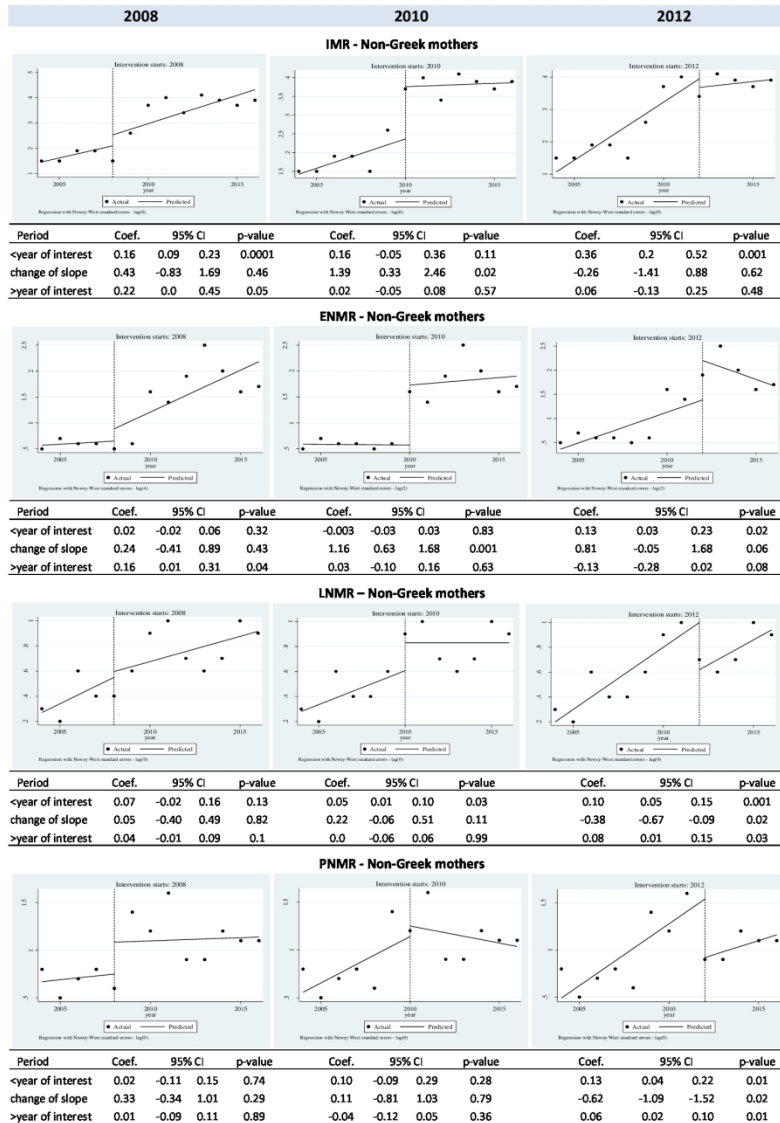
Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

60x81mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to Greek mothers.

140x198mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to non-Greek mothers.

140x198mm (300 x 300 DPI)

Suppl. Table 1. Infant deaths and total infant mortality rates (IMR) by place of residence (2004-2014).

Year	Infants born to mothers living in urban/semiurban areas		Infants born to mothers living in rural areas	
	Infant deaths (N)	Mortality rates/1000 livebirths	Infant deaths (N)	Mortality rates/1000 livebirths
2004	400	4.5	29	1.8
2005	383	4.2	26	1.6
2006	382	4.0	33	1.9
2007	377	3.9	20	1.2
2008	298	2.9	16	0.9
2009	344	3.4	27	1.5
2010	403	4.1	33	1.9
2011	326	3.5	31	2.2
2012	276	3.2	17	1.3
2013	334	4.2	11	0.8
2014	284	3.6	55	3.9

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Research checklist- STROBE Statement—checklist

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BMJ Open

Disparities of infant and neonatal mortality trends in Greece during the years of economic crisis by ethnicity, place of residence and human development index: a nationwide population study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-025287.R3
Article Type:	Research
Date Submitted by the Author:	30-May-2019
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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Epidemiology, Public health, Health policy, Global health
Keywords:	Neonates, Mortality rates, Infant deaths, perinatal care, financial crisis

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Manuscripts

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3 **Disparities of infant and neonatal mortality trends in Greece during the years of economic**
4 **crisis by ethnicity, place of residence and human development index: a nationwide**
5 **population study**
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12 Tania Siahaniidou, Nick Dessypris, Antonis Analitis, Constantinos Mihas, Evangelos Evangelou,
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ABSTRACT**OBJECTIVE**

To study trends of infant (IMR) and neonatal mortality rate in Greece during the period 2004-2016 and explore the role of sociodemographic factors in the years of crisis.

DESIGN

Nationwide individual data for livebirths and infant (0-11 months) deaths provided by the Hellenic Statistical Authority were examined using Poisson, joinpoint regression and Interrupted Time Series (ITS) analyses.

SETTING

Greece

PARTICIPANTS

All infant deaths (n=4862) over the 13-year period, of which 87.2% were born to Greek mothers, and respective livebirths.

MAIN OUTCOME MEASURES

Evolution of IMR (0-364 days), early (<7 days/ENMR), late (7-27 days/LNMR) neonatal and post neonatal (28-364 days/PNMR) mortality trends, by maternal nationality, place of residence and Human Development Index (HDI).

RESULTS

By Poisson regression, overall, during the study-period, among infants of Greek mothers, IMR and PNMR declined significantly (-0.9%; 95% CI -1.7% to -0.1% and -1.6%; -3.0% to -0.2% annually, respectively), albeit differentially by place of residence (IMR_{urban}: -2.1%; -2.9% to -1.3%, IMR_{rural}: +10.6%; 7.6% to 13.6%). By contrast, among infants of non-Greek mothers, the low starting IMR/ENMR/LNMR/PNMR increased significantly (max ENMR: +12.5%; 8.6% to 16.5%) leading to a non-significant time-trend pattern overall in Greece. The inverse associations of HDI with IMR, ENMR and PNMR were restricted to Greek mothers' infants.

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3 Joinpoint regression analyses among Greek mothers' infants indicated non-significant
4
5 increasing trends of IMR and ENMR following the crisis (+9.3%, 2012-2016, $p=0.07$ and
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7 +10.2%, 2011-2016, $p=0.06$, respectively). By contrast, the high (+17.1%; 8.1% to 26.9%,
8
9 $p=0.002$) IMR increases among non-Greek infants were restricted to 2004-2011 and
10
11 equalized to those of Greek mothers' infants thereafter. ITS analyses in preset years (2008,
12
13 2010, 2012) identified significantly increasing trends in IMR, LNMR and PNMR after 2012,
14
15 and in ENMR after 2010, among Greek mothers' infants.
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20 CONCLUSIONS

21
22 HDI and rural residence were significantly associated with IMR. The strongly decreasing IMR
23
24 trends among Greek-mothers' infants were stagnated after a lag time of ~four years of crisis
25
26 approximating the previously sharply increasing trends among non-Greeks.
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35 Strengths of this study

- 36
37 • Longest follow-up period of national data, as contrasted to previously Greek-based
38
39 studies.
- 40
41 • Maternal ethnicity is for first time considered in the analyses explaining part, if not
42
43 most, of the heterogeneity of trends through the study period.
- 44
45 • Three complimentary statistical methodologies were used to describe the overall
46
47 evolution of infant mortality and its components.
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54 Limitations

- 55
56 • Absence of a linkage system between birth and death data.
- 57
58 • Data on the role of biological factors or specific causes of infant death are missing.
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5 **Abbreviations:**
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7 IM; infant mortality
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10 IMR; infant mortality rates
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12 ENMR; early neonatal mortality rates
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14 LNMR; late neonatal mortality rates
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16 PNMR; post neonatal mortality rates
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18 HDI; Human Development Index
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20 ELSTAT; Hellenic Statistical Authority
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22 ITS; Interrupted Time Series
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Introduction

Socioeconomic factors have repeatedly been recognized as strong determinants of the health status of the population, including infants.¹⁻³ Economic indicators, such as the *per capita* Gross National Product, were suggested to be at least as important contributors of infant mortality (IM) as narrowly defined factors relating to provision of medical care, e.g. the relative number of doctors or hospital beds in a community.¹ Not surprisingly, the recent economic crisis of ~2008, has been linked with declines in population and child health reflected also by increased IM rates (IMR).^{4,5} It is worth noting that in European Union countries, even a minor 1% cut in government healthcare spending was associated with significant increases in all mortality metrics, including neonatal and post neonatal IM.⁶

On the contrary, associations between the crisis and increased mortality have been questioned in other studies showing that most indicators of population health, apart from those relevant to suicides and mental health, continued improving after crisis initiation.⁷⁻¹⁰ Moreover, the economic crisis has been associated with some beneficial effects, i.e. decline in rates of road traffic accidents, and smoking cessation.^{4,9} Reasonably, the impact of the crisis on health depends on several factors including the duration and intensity of the recession, the level of health care achieved prior to the recession and the type of austerity measures applied, but also on the type of the population studied with the most vulnerable groups being disproportionately affected.^{4,11,12} Due to the latter, it was proposed that studies should focus on analyzing separately the subgroups most influenced by the crisis instead of presenting results as averages in a population.⁴

Greece has been markedly affected and still suffering the recent economic crisis. Between 2008 and 2016, the country's GDP *per capita* dropped by 26%, unemployment rate increased by more than 200% (from 7.6% to 23.3%) and the median disposable income decreased by 35%.^{13,14} The GINI index, which measures income inequality, increased by 22% and the

1
2 proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016.
3
4
5 Total health expenditures and government expenditure on health care were both decreased
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7 by 34% per capita over the period 2008-2016,^{13,14} whereas unmet healthcare needs
8
9 increased.¹⁵ Besides, during the last years, Greece experienced large refugee flows^{16,17} with
10
11 an anticipated negative impact on the country's economy and population health indicators.
12
13
14 Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth
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16 and stillbirth rates, have been also observed;^{18,19} however, sparse data exist regarding the
17
18 potential association of the crisis with IMR. It has been initially reported that during the
19
20 period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period
21
22 whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to
23
24 the steady decrease observed during the preceding decade.^{20,21} Ecological correlations may
25
26 prone, however, to fallacies, whereas the different parts shaping the two main components
27
28 of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly
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30 examined along with other factors possibly influencing the infants' health, especially
31
32 socioeconomic status and access to health care delivery.
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34
35 The aims of the current study were to explore time trends in early (<7 days of life) and late
36
37 (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during
38
39 the period 2004-2016 after taking into account nationality and place of residence, as well as
40
41 changes in the Human Development Index (HDI) during the study period as a proxy of
42
43 individual and collective measures of socioeconomic impact and health care access.
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54 **Materials and Methods**

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56 Following personal contact and a signed agreement, individual data for all livebirths and
57
58 infant (0-11 months) deaths were provided by the Hellenic Statistical Authority (ELSTAT) for
59
60 a 13-year period (2004-2016) in two separate files: one including live births and a second

1
2 one, infant deaths; linkage of the two files was not possible as the personal identification
3
4 number was not available in ELSTAT. Information on maternal demographic characteristics,
5
6 such as nationality and place of residence, as well as on the infants' age at death, was also
7
8 provided.
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11 Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late
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13 neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective
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15 numbers of deaths over the number of livebirths per year. Annual percent of change (APC)
16
17 during the study period was initially estimated through univariate Poisson regression
18
19 analysis using the underlying population of each set as an offset variable. Subsequently, data
20
21 were stratified and analyzed by maternal nationality (Greek vs. non-Greek) and place of
22
23 residence (Urban/Semi-urban vs. Rural). Joinpoint regression analysis²² was thereafter
24
25 applied to automatically derive, by a software program, different segments in the mortality
26
27 evolution curves overall, as well as those by maternal nationality and place of residence. In
28
29 details, the Joinpoint regression analysis is applied to study varying trends over time in order
30
31 to identify the time point(s) in which the trend significantly changes. The location of the
32
33 joinpoint is not known a priori and is to be estimated from the data. Therefore, the software
34
35 takes trend data (e.g. IM rates) and fits the simplest joinpoint model based on the data. The
36
37 user supplies the minimum and maximum number of joinpoints. The algorithm starts with
38
39 the minimum number of joinpoint (e.g. 0 joinpoints, which is a straight line) and tests
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41 whether more joinpoints are statistically significant and must be added to the model (up to
42
43 that maximum number). Significance is tested using a Monte Carlo Permutation method. In
44
45 all models examined in this study, a minimum number of 0 joinpoints and a maximum one of
46
47 2 joinpoints were tested. Interrupted Time Series (ITS) analyses were also undertaken as a
48
49 sensitivity analysis to further explore the effect of crisis on IMR and its components in
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51 alternative prespecified years, notably 2008, considered to indicate the initiation of the crisis
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3 in Greece -as the value of the Gross Domestic Product of the country was maximum at that
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5 year but dropped afterwards (Source: Aggregate National Accounts)-, and in two successive
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7 periods two years apart (2010 and 2012), to control for possible time lags in observing the
8
9 impact of the crisis. All ITS models were verified and appropriately adjusted for possible
10
11 auto-correlation; autoregressive integrated moving - average models were used to control for
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13 autocorrelation and to estimate treatment effects over multiple periods. In our ITS analysis a
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15 slope “<year of interest” is fitted until the introduction of the crisis, “>year of interest”
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17 represents the change in the level of the mortality immediately following the initiation of the
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19 crisis and “change of slope” represents the differences between pre and post crisis intervention
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21 slopes.
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25
26 Human development index (HDI) is a summary measure of average achievements of a
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28 country’s population in three areas including life expectancy, education and *per capita*
29
30 income indicators. Annual HDI values for the underlying populations in the year of death
31
32 were extracted from the United Nations Development Program website
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34 (<http://hdr.undp.org/en/composite/HDI>), whereas Poisson regression analysis was used to
35
36 explore the association of one standard deviation of HDI with total IM and its components.
37
38 All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata
39
40 software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13.
41
42 College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression
43
44 Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch,
45
46 Surveillance Research Program, National Cancer Institute).

55 **Patient involvement**

56
57 No patients were involved in setting the research question or the outcome measures, nor
58
59 were they involved in developing plans for design or implementation of the study. No
60

1
2 patients were asked to advise on interpretation or writing up of results. There are no plans
3
4 to disseminate the results of the research to study participants or the relevant patient
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6 community.
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11
12 **Ethical approval:** Not required.
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16 17 **Results**

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19 The annual average number of livebirths during the study period was 105077, ranging from a
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21 high 118302 (2008) to a low 91847 livebirths in 2015. The annual average proportion of
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23 Greek mothers was 83.7%, whereas the remaining were mainly economic migrants. During
24
25 the period 2004-2016, a total of 4862 infant deaths were recorded of whom 4238 (87.2%)
26
27 were of infants born to Greek mothers, whereas among the remaining 615 deaths of infants
28
29 born to non-Greek mothers, 298 (48.5%) were of infants born to Albanian mothers, 146
30
31 (23.7%) of infants born to mothers from Balkan countries and countries of the former Soviet
32
33 Union, 77 (12.5%) from Asia, 47 (7.6%) from countries of the European Union or other
34
35 developed countries and 47 (7.6%) from Africa. During the early and late neonatal period,
36
37 2107 (43.3%) and 1136 (23.4%) deaths occurred, respectively, whereas another 1617
38
39 (33.3%) of deaths were recorded in the post neonatal period. The annual average IMR was
40
41 3.5 over 1000 livebirths, whereas the corresponding figures for the early, late and post
42
43 neonatal period were 1.5‰, 0.8‰ and 1.2‰ respectively. The number of livebirths and
44
45 infant deaths, total IMR per 1000 livebirths in infants born to Greek and non-Greek mothers,
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47 as well as HDI values, in Greece, during the study period, are shown in Table 1. Moreover,
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49 infant deaths and total infant mortality rates (IMR) by place of residence (Urban/Semi-urban
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51 vs. Rural) are shown in Suppl. Table 1.
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3 Of note, in the beginning of the study period in 2004, notably well before the initiation of
4
5 the crisis, IMR and its components were 2- to 4-fold higher among infants born to Greek
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7 mothers in comparison with rates in infants born to non-Greek origin mothers. During the
8
9 subsequent 4-5 years, however, rates among Greeks followed downward trends, whereas
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11 among non-Greeks inflated reaching almost similar values to those observed in infants born
12
13 to Greek mothers (Figure 1).
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17 Overall, during the study-period, among infants born to Greek mothers, Poisson regression
18
19 analyses showed decreasing trends in IMR and PNMR (-0.9%; 95% CI -1.7% to -0.1% and -
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21 1.6%; -3.0% to -0.2% annually, respectively, $p=0.02$ for each), whereas no significant change
22
23 in ENMR and LNMR was observed (Table 2). Interestingly, mortality trends changed
24
25 differentially by place of residence; significant decline of IMR trends (-2.1%; -2.9% to -1.3%
26
27 annually, $p<0.0001$) and all its components was observed among infants born to Greek
28
29 mothers living in urban areas whereas, among infants born to Greek mothers in rural areas,
30
31 a significant increase of IMR (+10.6%; 7.6% to 13.6% annually, $p=0.002$), ENMR (+24.1%;
32
33 17.0% to 31.5% annually, $p<0.0001$) and LNMR trend (+12.7%; 6.5% to 19.2% annually,
34
35 $p<0.0001$) was observed (Table 2). By contrast, among infants of non-Greek mothers, the
36
37 low starting IMR increased significantly (+9.4%; 6.9% to 11.9% annually, $p<0.0001$), due to
38
39 significant increases of ENMR, LNMR and PNMR (max ENMR: +12.5%; 8.6% to 16.5%
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41 annually, $p<0.0001$) leading to a non-significant pattern of IMR evolution for Greece overall
42
43 ($p=0.50$) (Table 2). Further analysis by nationality of non-Greek mothers showed significant
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45 increases of IMR trends in all ethnic groups with average annual percent change 7.6% (95%
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47 CI; 4.2% to 11.1%) in infants born to Albanian mothers, 8.6% (3.7% to 13.8%) in infants born
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49 to mothers from Balkan countries and countries of the former Soviet Union, 9.4% (2.8% to
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51 16.3%) in infants born to mothers from Asia, 9.4% (1.1% to 18.3%) in infants born to
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53 mothers from countries of the European Union or other developed countries, and 21.1%
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3 (11.0% to 32.3%) in infants born to mothers from Africa. HDI trends increased significantly,
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5 by 0.1% (95% CI 0.06% to 0.13%) annually, during the study period. Inverse associations of
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7 HDI with IMR, ENMR and PNMR, restricted to Greek mothers' infants, were observed (Table
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12 In order to examine whether IMR, in our study population, might have influenced by any
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14 variation in the registration of births in cases of uncertain viability, we analyzed separately
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16 the infant deaths in the first day of life; trends of IMR in this age group, over the study
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18 period, were non-significant (average annual percent change: -1.22%; 95% CI: -3.79% to
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20 1.42%; $p=0.36$).

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24 By joinpoint regression analyses, a break was identified in the IMR curve among infants born
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26 to Greek mothers restricting the decreasing IMR trend to the period 2004-2012 (-4.5%; 95%
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28 CI -7.6% to -1.3% annually, $p=0.01$); a significant decline in ENMR trend till 2011 (-6.5%; 95%
29
30 CI -11.4% to -1.4% annually, $p=0.02$) was also found (Table 3). Of note, however, in the most
31
32 recent study period following the crisis, non-significant increasing trends of IMR (2012-2016:
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34 +9.3% annually, $p=0.07$) and ENMR (2011-2016: +10.2% annually, $p=0.06$) were observed. By
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36 contrast, among infants born to non-Greek mothers, the high IMR increases (+17.1%; 95% CI
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38 8.1% to 26.9% annually, $p=0.002$) were restricted to the period 2004-2011 with no
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40 statistically significant change thereafter (2011-2016); no break was identified for ENMR
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42 curve. Significant increases in IMR and ENMR trends after the year 2008 were observed in
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44 the total study population, whereas no break was found for LNMR and PNMR measures in
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46 Greeks, non-Greeks or the total study population (Table 3).

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48
49 The results of ITS analyses in the preset years 2008, 2010 and 2012 are shown in Figures 2
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51 and 3. Compared to the joinpoint regression showing non-significant increases in IMR from
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53 2012 to 2016 for infants born to Greek mothers, ITS analysis showed a significant increase in
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55 IMR ($p=0.0001$) in this population during the same time period and further identified

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3 significant increases in LNMR ($p=0.0004$) and PNMR trends ($p=0.03$). As regards the non-
4
5 significant increases of ENMR trends after the year 2011 by joinpoint regression in infants
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7 born to Greek mothers ($p=0.06$), ITS analysis showed a non-significant increase during the
8
9 post 2012 time period ($p=0.07$); however, a significant increase during the post 2010 time
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11 period in these infants was observed ($p=0.01$) (Figure 2). In infants born to non-Greek
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13 mothers, while a significant increase in IMR trends was found by joinpoint regression
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15 analyses during the period 2004-2011, by ITS analyses -depending on when the year of
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17 interest was being defined (2010 or 2012)- the increase was either not significant (2004-
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19 2010, $p=0.11$) or significant (2004-2012, $p=0.001$); no change in IMR was identified by ITS
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21 analysis over the 2010-2016 or 2012-2016 time periods in non-Greek mothers' infants
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23 (Figure 3).
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31 Discussion

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33 Trends of neonatal and infant mortality in Greece, spanning from year 2004 -before the
34
35 initiation of crisis in 2008- to year 2016, are not homogeneous, given significant increases in
36
37 the relatively small proportion of infants born to non-Greek nationality mothers as
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39 contrasted to declining IMR trends among Greek mothers' infants, differentials by place of
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41 residence and also increases in IM indices among Greek mothers' infants noted ~four years
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43 after the crisis initiation. Specifically, the "brake" of 2012 identified, by joint point regression
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45 analysis, non-significant increases of ~10% annually, in IMR and ENMR trends, whereas by ITS
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47 analyses, significant increases in IMR, LNMR and PNMR trends were observed thereafter
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49 among infants born to Greek mothers, a fact indicating how sensitive the results are
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51 depending on the statistical method used. Changes in HDI during the study period were also
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53 reflected in the inverse associations of HDI with ENMR and IMR, but also PNMR, among
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55 infants born to Greek mothers.
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3 Strengths of the present investigation, as contrasted to previously Greek-based published
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5 studies,^{9,18,20,21,23} include the longest follow-up period of national data, namely since 2004,
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7 before the crisis, when the first data on maternal ethnicity became electronically available,
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9 to the latest available year 2016. Of great importance is also the fact that, for the first time,
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11 the maternal ethnicity was considered in the analyses explaining part, if not most, of the
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13 heterogeneity of trends through the study period. To this end, three complimentary
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15 statistical methodologies were used to describe the overall evolution depicted in Figure 1.
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17 Thus, we were able to enhance the validity of the results pertaining to the study of the
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19 evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association
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21 with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which
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23 individual data have been available on a nationwide level among both deaths and livebirths
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25 during the study period. Calculation of IMR and its components was based on the number of
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27 livebirths; yet, the absence of a linkage system between birth and death data consists a
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29 limitation of the study. The absence of a linkage system, as well as that of other official
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31 registries in Greece, has not allowed use of known determinants of socioeconomic
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33 deprivation or social coherence, such as parental education, employment/occupation,
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35 marital status, family income and household size. Neither were data on the role of biological
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37 factors, such as parental age, gestational age and birthweight, or multiplicity of pregnancy
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39 available for both the livebirths and deaths series.^{5,19,24} Besides, the study period, with
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41 available information on maternal nationality and place of residence, was rather short leading
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43 to ITS analyses with few data points; however, ITS analysis can be used even for few
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45 observations; no log-transformation is needed but the results should be interpreted with
46
47 caution as the power depends on various factors.²⁵ Lastly, analyses by specific cause of infant
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49 death were not set among the outcome measures of this study.
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3 Assessing migration as a determinant of perinatal health outcome and infant death in the
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5 developed countries is a complex undertaking resulting in conflicting results of published
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7 studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor
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9 for unfavorable perinatal outcomes and increased neonatal and infant mortality,^{18,26-33}
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11 especially if it coincides with a financial crisis, as was the case in Greece. Factors possibly
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13 contributing to the increased risk for poorer outcomes among children born to migrants
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15 include socioeconomic disadvantage, poor communication, discrimination, reduced
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17 utilization of health facilities, low quality of care, but also stress and consanguinity or
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19 differing attitudes to screening and termination of pregnancy associated with preterm birth,
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21 low birth weight or congenital anomalies and lethal inherited diseases.^{26,30,34-36} By contrast,
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23 other studies present similar or even better perinatal health outcomes among some migrant
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25 groups than among natives (“healthy migrant effect/paradox”).^{26-28,37,38} Refugees have been
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27 recognized as the most vulnerable group suffering increased severe neonatal morbidity and
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29 infant mortality risk,^{26,28} although no absolutely clear pattern regarding refugee or non-
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31 refugee status among migrants has been identified.³⁴
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34 In our study, starting rates of IMR and its components among infants born to non-Greek
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36 mothers were lower compared to those of Greek mothers. Of note, the ratio of non-Greek
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38 infants among live births during 2009-2016 vs. 2004-2008 was only 1.32, whereas the
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40 respective figure among infant deaths was almost 3-fold (data not shown). Actually, in the
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42 pre-crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most
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44 of them of Albanian nationality living for many years, or even born, in Greece. After 2008,
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46 Greece experienced an influx of refugees with the majority of them fleeing from war and
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48 terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other
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50 countries.^{16,17} It could be suggested that changes in the homogeneity of foreign mothers
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52 during the study period, in association with the country’s economic difficulties, might have
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2 led from the “healthy migrant effect”, observed before 2008, to the deterioration of IM
3 indicators and IMR trends, afterwards, in infants born to non-Greek mothers. We did
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5 observe significant increases in IMR trends in all ethnic groups of non-Greek mothers during
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7 the study period, especially in infants born to mothers from Africa; however as the numbers
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9 by individual maternal nationality were rather small, this issue needs to be further studied.
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14 Simultaneously with immigration to/through Greece, the country experienced the third
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16 wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left
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18 Greece since the onset of the economic crisis, in 2008, seeking new opportunities and
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20 employment in other countries, mainly Germany, the United Kingdom and the
21
22 Netherlands.^{39,40} The current emigration wave of Greeks involved mostly highly-educated
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24 people (the so called “brain-drain”) of young age, leading to a decrease in the number of
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26 Greek women of childbearing age.⁴¹ This fact, along with the decrease in the fertility rate by
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28 almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual
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30 number of livebirths in Greece by almost 23% during the period of the economic crisis.^{41,42}
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32 Furthermore, the flow of mostly affluent and well educated people going outside Greece
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34 could also contribute to increases in IMR among Greek children following the crisis.
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42 Indeed, the strongly decreasing IMR trends among Greek infants were stagnated after a lag
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44 time of ~four years of crisis and equalized with the previously sharply increasing trends
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46 among non-Greek maternal nationality infants; this time lag is reasonable⁴³ and in line with
47
48 previous findings showing that following reductions in the government healthcare spending
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50 in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4 and 5
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52 years later, respectively.⁶ The irony is that the period 2012-2016, during which the crisis was
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54 deepening^{13,14} and stricter economic austerity measures were applied,⁴⁴ disparities gap in
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56 IMR trends diminished against the Greek population; IMR trends deteriorated only in infants
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2 born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends
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4 approached an anelastic highest value up to 2011 with no statistically significant change
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6 thereafter.
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10 Disparities in IMR still exist across geographic areas even in well developed countries; i.e.
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12 IMR in the United States vary by urbanization level of maternal residency being lowest in
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14 large urban counties but highest in rural areas.⁴⁵ Rural women may face health challenges
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16 related to geographic barriers to care (less timely and/or appropriate care) and physician
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18 shortages, but they may also present differences in a number of socioeconomic and
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20 demographic risk factors, such as less education, lower income, younger age at pregnancy,
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22 or greater number of children, in comparison with their urban counterparts.^{46,47} The
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24 increasing IMR trends during the study period in infants born to Greek mothers living in rural
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26 areas, as opposed to the declining IMR trends in those born to Greek mothers living in
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28 urban/semi urban areas, is worrisome; specific causes should be further studied and
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30 addressed. As regards infants born to non-Greek mothers, the increasing IMR trends despite
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32 living in urban areas can be explained by previous reports showing that other risk factors, i.e.
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34 young maternal age (<20 years) or maternal ethnic minority, may be more powerful than
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36 place of residence.⁴⁷
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40 Among the three IMR components, ENMR seemed to be the most “sensitive” in reflecting
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42 adverse impacts on child health. Specifically, ENMR was overall positively associated with
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44 rural place of residence of Greek mothers' children and also presented the most sizeable
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46 increase among IM indices in non-Greeks (Table 2). Moreover, among the three IM
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48 components, ENMR was the first or the only one, -depending on the statistical method used-
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50 , that increased after the crisis initiation in infants born to Greek mothers. ENMR, in
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52 developed countries, including Greece, represents more than 70% of neonatal deaths on
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54 account mainly of prematurity/low birth weight and congenital anomalies.^{14,48-51} Actually, it
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3 reflects perinatal health and care during pregnancy and labor, and also postnatal care in the
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5 first week of life.⁵⁰ Increased incidence of impaired perinatal parameters including low birth
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7 weight, prematurity, and increased maternal age and rate of caesarian section, have been
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9 reported during the years of the economic decline in Greece.^{18,19} Cuts in public health
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11 expenditures between 2008 and 2016, reduction in health care workforce and pediatric
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13 nurses, as well as reduction in the number of obstetrics beds, obstetricians and midwives (-
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15 45.5%, -60.2% and -27.5%, respectively)¹⁴ could possibly explain, at least in part, the
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17 observed positive ENMR trends during the post-crisis period in Greece.
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22 The exact mechanisms leading to the disparities in trends of neonatal and infant mortality
23
24 observed in this study remain to be further explored. Specific maternal, family and infant
25
26 features, including detailed and punctual information on the causes of infant deaths, would
27
28 have shed more light on the links between IMR trends and socioeconomic factors but were
29
30 beyond the scope of this article and left for future research. Meanwhile, policies and
31
32 programs should be implemented to mitigate the negative impact of the crisis on population
33
34 and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of
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36 low income, or rural place of residence, should be specifically addressed and their rights to
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38 health protected. Barriers in the access of refugees to the Greek health care system have
39
40 been identified; they are mostly related to language, culture, and inadequate information
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42 about the healthcare system, but also include difficulties in the coordination of Health
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44 Services, transportation problems, issues in obtaining expertise medical assessment in the
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46 camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for
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48 health and social care services, and administrative barriers, among others.⁵² In response, the
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50 Greek government and several Non-Governmental Organizations initiated commendable
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52 actions, i.e. National Health System services free of charge for uninsured and vulnerable
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54 social groups including asylum seekers, translation services in public hospitals, access to
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2 specialist care/treatment with Gynecologists (mostly women), midwives, dentists,
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4 psychologists, and psychiatrists being lately included in the camp clinics;⁵² these actions may
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6 have prevented deterioration of IMR which are being kept at steady levels after 2011-2012
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8 in infants of non-Greek mothers; efforts should be continued and intensified, however, as to
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10 ensure equity with local populations. Strong governmental integration policy for minorities
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12 paired with initiatives to improve social coherence, a deeply rooted mechanism for
13
14 protection of health among those in need in the Greek society, along with further
15
16 improvements in primary health care delivery could help to alleviate the cost in infant lives
17
18 and ensure healthy adulthood.^{32,51} Irrespective of the crisis, improvements in the quality of
19
20 perinatal and neonatal care, including centralization of very preterm deliveries,
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22 establishment of regional perinatal centers, monitoring of the implementation of evidence-
23
24 based practices in maternity and neonatal units, as well as increase in health expenditures,
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26 health care workforce, number of doctors and midwives/nurses, could decrease ENMR,
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28 eventually leading to overall decrease in IMR in Greece.⁵⁰
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39 REFERENCES

- 41 1. Petridou E, Valadian I, Trichopoulos D, Tzonou A, Kyriopoulos Y, Matsaniotis N. Medical
42 services and socioeconomic factors: Determinants of infant mortality in Greece.
43
44 *Hygie*1989;3:20-3.
45
46
- 47 2. WHO. The determinants of health. <http://www.who.int/hia/evidence/doh/en> (Date of
48 access: 30/5/2018)
49
50
51
- 52 3. Zylbersztejn A, Gilbert R, Hjern A, Wijlaars L, Hardelid P. Child mortality in England
53 compared with Sweden: a birth cohort study. *Lancet* 2018;391(10134):2008-2018.
54
55
56
57
58
59
60
doi:10.1016/S0140-6736(18)30670-6.

- 1
2
3 4. Rajmil L, Fernandez de Sanmamed MJ, Choonara I, et al; International Network for
4
5 Research in Inequalities in Child Health (INRICH). Impact of the 2008 economic and financial
6
7 crisis on child health: a systematic review. *Int J Environ Res Public Health* 2014;11:6528-
8
9 46.doi:10.3390/ijerph110606528.
- 10
11
12 5. Glonti K, Gordeev VS, Goryakin Y, Reeves A, Stuckler D, McKee M, Roberts B. A systematic
13
14 review on health resilience to economic crises. *PLoS One* 2015;10:e0123117.
15
16 doi:10.1371/journal.pone.0123117.
- 17
18
19 6. Budhdeo S, Watkins J, Atun R, Williams C, Zeltner T, Maruthappu M. Changes in
20
21 government spending on healthcare and population mortality in the European union, 1995–
22
23 2010: a cross-sectional ecological study. *J R Soc Med* 2015;108:490-8.
24
25 doi:10.1177/0141076815600907.
- 26
27
28 7. Tapia Granados JA, Rodriguez JM. Health, economic crisis, and austerity: A comparison of
29
30 Greece, Finland and Iceland. *Health Policy* 2015;119:941-53.
31
32 doi:10.1016/j.healthpol.2015.04.009.
- 33
34
35 8. Regidor E, Barrio G, Bravo MJ, de la Fuente L. Has health in Spain been declining since the
36
37 economic crisis? *J Epidemiol Community Health* 2014;68:280-2.doi:10.1136/jech-2013-
38
39 202944.
- 40
41
42 9. Laliotis I, Ioannidis JPA, Stavropoulou C. Total and cause-specific mortality before and
43
44 after the onset of the Greek economic crisis: an interrupted time-series analysis. *Lancet*
45
46 *Public Health* 2016;1: e56–e65. doi:10.1016/S2468-2667(16)30018-4.
- 47
48
49 10. Parmar D, Stavropoulou C, Ioannidis JP. Health outcomes during the 2008 financial crisis
50
51 in Europe: systematic literature review. *BMJ* 2016;354:i4588. doi:10.1136/bmj.i4588.
- 52
53
54 11. O'Donnell C, Burns N, Dowrick C, Lionis C, MacFarlane A; RESTORE team. Health-care
55
56 access for migrants in Europe. *Lancet* 2013; 382:393. doi: 10.1016/S0140-6736(13)61666-9.
57
58
59
60

- 1
2
3 12. Karanikolos M, Heino P, McKee M, Stuckler D, Legido-Quigley H. Effects of the Global
4
5 Financial Crisis on Health in High-Income OECD Countries: A Narrative Review. *Int J Health*
6
7 *Serv* 2016;46:208-40. doi: 10.1177/0020731416637160.
8
9
10 13. Organisation for Economic Co-operation and Development OECD data.
11
12 <https://data.oecd.org> (Date of access: 30/5/2018) (2016).
13
14
15 14. Hellenic Statistical Authority *Statistics*. www.statistics.gr (Date of access: 30/5/2018)
16
17 (2016).
18
19 15. Zavras D, Zavras AI, Kyriopoulos II, Kyriopoulos J. Economic crisis, austerity and unmet
20
21 healthcare needs: the case of Greece. *BMC Health Serv Res* 2016;16:309.
22
23 doi:10.1186/s12913-016-1557-5.
24
25
26 16. European Union. The EU and the migration crisis, July 2017,
27
28 <http://publications.europa.eu>
29
30
31 17. Mertens E, Rockenschaub G, Economopoulou A, Kreidl P. Assessment of public health
32
33 issues of migrants at the Greek-Turkish border, April 2011. *Euro Surveill* 2012 Jan 12;17(2).
34
35 pii: 20056.
36
37
38 18. Zografaki I, Papamichail D, Panagiotopoulos T. Adverse effect of the financial crisis in
39
40 Greece on perinatal factors. *Eur J Public Health* 2018 [Epub ahead of print]. doi:
41
42 10.1093/eurpub/cky078.
43
44
45 19. Sdoná E, Papamichail D, Ragkou E, Briana DD, Malamitsi-Puchner A, Panagiotopoulos T.
46
47 Greek economic crisis and impaired perinatal parameters: experience from a public
48
49 maternity hospital. *J Matern Fetal Neonatal Med* 2018;31:2371-5.
50
51 doi:10.1080/14767058.2017.1342803.
52
53
54 20. Michas G, Varytimiadi A, Chasiotis I, Micha R. Maternal and child mortality in Greece.
55
56 *Lancet* 2014;383:691-2. doi:10.1016/S0140-6736(14)60251-8.
57
58
59
60

- 1
2
3 21. Filippidis F, Gerovasili V, Millett C, Tountas Y. Medium-term impact of the economic crisis
4 on mortality, health-related behaviours and access to healthcare in Greece. *Sci Rep*
5 2017;7:46423. doi:10.1038/srep46423.
6
7
8
9
10 22. Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with
11 applications to cancer rates. *Stat Med* 2000;19:335-51. PMID:10649300
12
13
14 23. Simou E, Koutsogeorgou E. Effects of the economic crisis on health and healthcare in
15 Greece in the literature from 2009 to 2013: a systematic review. *Health Policy* 2014;115:111-
16 9. doi: 10.1016/j.healthpol.2014.02.002.
17
18
19
20 24. Petridou ET, Georgakis MK, Erdmann F, et al. Advanced parental age as risk factor for
21 childhood acute lymphoblastic leukemia: results from studies of the Childhood Leukemia
22 International Consortium. *Eur J Epidemiol* 2018. doi:10.1007/s10654-018-0402-z. [Epub
23 ahead of print].
24
25
26
27 25. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation
28 of public health interventions: a tutorial. *Int J Epidemiol* 2017;46(1):348-55. doi:
29 10.1093/ije/dyw098.
30
31
32 26. Gissler M, Alexander S, MacFarlane A, et al. Stillbirths and infant deaths among migrants
33 in industrialized countries. *Acta Obstet Gynecol Scand* 2009;88:134-
34 48. doi:10.1080/00016340802603805.
35
36
37
38 27. Gagnon AJ, Zimbeck M, Zeitlin J, et al. Migration to western industrialized countries and
39 perinatal health: a systematic review. *Soc Sci Med* 2009;69:934-46.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54 28. Wanigaratne S, Cole DC, Bassil K, et al. Severe Neonatal Morbidity Among Births to
55 Refugee Women. *Matern Child Health J* 2016;20:2189-98. doi:10.1007/s10995-016-2047-4.
56
57
58
59
60

- 1
2
3 29. Puthussery S. Perinatal outcomes among migrant mothers in the United Kingdom: Is it a
4 matter of biology, behaviour, policy, social determinants or access to health care? *Best Pract*
5 *Res Clin Obstet Gynaecol* 2016;32:39-49. doi:10.1016/j.bpobgyn.2015.09.003.
6
7
8
9
10 30. Wanner P, Bollini P. The contribution of the foreign population to the high level of infant
11 mortality in Switzerland: a demographic analysis. *BMC Pregnancy Childbirth* 2017;17:151.
12 doi:10.1186/s12884-017-1332-6.
13
14
15
16
17 31. Cantarutti A, Franchi M, Monzio Compagnoni M, Merlino L, Corrao G. Mother's
18 education and the risk of several neonatal outcomes: an evidence from an Italian
19 population-based study. *BMC Pregnancy Childbirth* 2017;17:221. doi:10.1186/s12884-017-
20 1418-1.
21
22
23
24
25
26
27 32. Bollini P, Pampallona S, Wanner P, Kupelnick B. Pregnancy outcome of migrant women
28 and integration policy: a systematic review of the international literature. *Soc Sci Med*
29 2009;68:452-61. doi:10.1016/j.socscimed.2008.10.018.
30
31
32
33
34 33. Gotsens M, Malmusi D, Villarroel N, et al. Health inequality between immigrants and
35 natives in Spain: the loss of the healthy immigrant effect in times of economic crisis. *Eur J*
36 *Public Health* 2015;25:923-9. doi:10.1093/eurpub/ckv126.
37
38
39
40
41 34. Nybo Andersen AM, Gundlund A, Villadsen SF. Stillbirth and congenital anomalies in
42 migrants in Europe. *Best Pract Res Clin Obstet Gynaecol* 2016;32:50-9.
43 doi:10.1016/j.bpobgyn.2015.09.004.
44
45
46
47
48 35. Di Renzo GC, Tosto V, Giardina I. The biological basis and prevention of preterm birth.
49 *Best Pract Res Clin Obstet Gynaecol* 2018. doi:10.1016/j.bpobgyn.2018.01.022. [Epub ahead
50 of print].
51
52
53
54
55 36. Wanigaratne S, Cole DC, Bassil K, Hyman I, Moineddin R, Urquia ML. The influence of
56 refugee status and secondary migration on preterm birth. *J Epidemiol Community Health*
57 2016;70:622-8. doi:10.1136/jech-2015-206529.
58
59
60

- 1
2
3 37. Kirby RS. Perinatal outcomes and nativity: does place of birth really influence infant
4 health? *Birth* 2011;38:354-6. doi:10.1111/j.1523-536X.2011.00505.x.
5
6
7 38. Sdoná E, Papamichail D, Ragkou E, et al. Migration status and perinatal parameters in a
8 Greek public maternity hospital: an illustration of the "healthy immigrant effect". *J Matern*
9 *Fetal Neonatal Med* 2017. doi: 10.1080/14767058.2017.1371131. [Epub ahead of print].
10
11
12
13
14 39. Eurostat, "Emigration by age group, sex and citizenship".
15 http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=migr_emi1ctz&lang=en(last
16 updated: 04/04/2018).
17
18
19
20
21 40. Cavounidis J. The changing face of emigration: Harnessing the potential of the New
22 Greek Diaspora. Washington, DC: Migration Policy Institute, 2015.
23
24
25
26 41. Vrachnis N, Vlachadis N, Iliodromiti Z, Vlachadi M, Creatsas G. Greece's birth rates and
27 the economic crisis. *Lancet* 2014;383:692-3. doi: 10.1016/S0140-6736(14)60252-X.
28
29
30
31 42. Eurostat, "Fertility indicators". [http://appsso.eurostat.ec.europa.eu/nui/show.](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en)
32 [do?dataset=demo_find&lang=en](http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=demo_find&lang=en) (last updated: 20/09/2018)
33
34
35
36 43. Karanikolos M, Mladovsky P, Cylus J, et al. Financial crisis, austerity, and health in
37 Europe. *Lancet* 2013;381:1323-31. doi:10.1016/S0140-6736(13)60102-6.
38
39
40
41 44. Burki T. Health under austerity in Greece. *Lancet* 2018;391:525-6. doi:10.1016/S0140-
42 6736(18)30242-3.
43
44
45
46 45. Ely DM, Driscoll AK, Mathews TJ. Infant mortality rates in rural and urban areas in the
47 United States, 2014. *NCHS data brief*, No 285. Hyattsville, MD: National Center for Health
48 Statistics, 2017.
49
50
51
52
53 46. Van de Poel E, O'Donnell O, Van Doorslaer E. What explains the rural-urban gap in infant
54 mortality: household or community characteristics? *Demography* 2009;46:827-
55 50. doi:org/10.1353/dem.0.0074.
56
57
58
59
60

- 1
2
3 47. Harris DE, Aboueissa AM, Baugh N, Sarton C. Impact of rurality on maternal and infant
4
5 health indicators and outcomes in Maine. *Rural Remote Health* 2015;15:3278.
6
7 48. Heron M. Deaths: Leading Causes for 2015. *Natl Vital Stat Rep* 2017;66:1-76.
8
9
10 49. Roncancio CP, Misnaza SP, Peña IC, Prieto FE, Cannon MJ, Valencia D. Trends and
11
12 characteristics of fetal and neonatal mortality due to congenital anomalies, Colombia 1999-
13
14 2008. *J Matern Fetal Neonatal Med* 2018;31:1748-55. doi:10.1080/14767058.2017.1326901.
15
16
17 50. Lehtonen L, Gimeno A, Parra-Llorca A, Vento M. Early neonatal death: A challenge
18
19 worldwide. *Semin Fetal Neonatal Med* 2017;22:153-60. doi:10.1016/j.siny.2017.02.006.
20
21
22 51. Alexander M, Harding M, Lamarche C. Quantifying the impact of economic crises on
23
24 infant mortality in advanced economies. *Applied Economics* 2011; 43: 3313–23.
25
26 doi:10.1080/00036840903559620.
27
28
29 52. Kotsiou OS, Kotsios P, Srivastava DS, Kotsios V, Gourgoulisanis KI, Exadaktylos AK. Impact
30
31 of the Refugee Crisis on the Greek Health care System: A Long Road to Ithaca. *Int J Environ*
32
33 *Res Public Health* 2018;15(8). pii:E1790. doi: 10.3390/ijerph15081790.
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41 **Contributors:** EP and GC were involved in the initial conception of the study. All authors
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43 contributed to the design, analysis and interpretation of data. TS, ND and EP developed the
44
45 first draft of the manuscript and all authors critically revised it and approved the final
46
47 version. ND, AA and CM performed the statistical analyses; EE reviewed statistics and
48
49 contributed significantly for ITS analyses. All authors agree to be accountable for all aspects
50
51 of the work in ensuring that questions related to the accuracy or integrity of any part of the
52
53 work are appropriately investigated and resolved. The corresponding author ensures that all
54
55 the journal's administrative requirements are properly completed.
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3 **Acknowledgements:** ELSTAT has provided individual anonymized data.
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7 **Data sharing:** Data are available upon request from ELSTAT
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10 (<http://www.statistics.gr/el/statistical-data-request>)
11
12

13 14 15 **Funding Statement**

16
17 This research received no specific grant from any funding agency in the public, commercial
18 or not-for-profit sectors'.
19
20

21 22 23 24 **Competing interests statement**

25
26 All authors have completed the ICMJE uniform disclosure form at
27 www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the
28 submitted work; no financial relationships with any organizations that might have an interest
29 in the submitted work in the previous three years; no other relationships or activities that
30 could appear to have influenced the submitted work.
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43 **Figure Legends**

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46 **Figure 1.** Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-
47 2016) overall and by maternal nationality.
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52 **Figure 2.** Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late
53 (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of
54 interest (2008, 2010 and 2012) in infants born to Greek mothers.
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3 **Figure 3.** Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late
4 (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of
5 interest (2008, 2010 and 2012) in infants born to non-Greek mothers.
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Table 1. Livebirths, infant deaths, total infant mortality rates (IMR) per 1000 livebirths in infants born to Greek and non-Greek mothers, and Human Development Index (HDI), in Greece during the period 2004-2016.

Year	Infants born to Greek mothers			Infants born to non-Greek mothers			HDI
	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths	Livebirths (N)	Infant deaths (N)	Mortality Rates/1000 livebirths	
2004	88805	403	4.5	16825	26	1.5	0.835
2005	89819	383	4.3	17678	26	1.5	0.845
2006	92590	379	4.1	19396	36	1.9	0.851
2007	91462	359	3.9	20412	38	1.9	0.849
2008	96329	281	2.9	21931	32	1.5	0.857
2009	95640	307	3.2	22244	58	2.6	0.858
2010	93209	355	3.8	21351	80	3.7	0.856
2011	87445	282	3.2	18680	74	4.0	0.852
2012	84868	241	2.8	15153	52	3.4	0.854
2013	80938	292	3.6	13063	53	4.1	0.856
2014	79985	298	3.7	12144	47	3.9	0.864
2015	79919	320	4.0	11919	44	3.7	0.866
2016	80166	338	4.2	12721	49	3.9	0.868

*excluding missing maternal nationality values.

Table 2. Poisson regression derived changes and 95% Confidence Intervals (CI) of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR): Annual Percent of Change (APC) for place of residence and maternal nationality (2004-2016); Percept of Change (PC) for 1 Standard Deviation of Human Development Index (HDI) controlling for year of birth.

	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	-0.9 (-1.7,-0.1)	0.02	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	-1.6 (-3.0,-0.2)	0.02
Non-Greek	615	9.4 (6.9,11.9)	<.0001	258	12.5 (8.6,16.5)	<.0001	138	8.0 (3.1,13.2)	0.001	218	4.4 (0.6,8.4)	0.02
All*	4862	0.3 (-0.5, 1.0)	0.50	2107	0.9 (-0.3,2.1)	0.13	1136	0.4 (-1.2,2.0)	0.65	1617	-0.9 (-2.2,0.5)	0.20
Urbanization												
Urban-Semi urban												
Greek	3850	-2.1 (-2.9, -1.3)	<.0001	1738	-2.0 (-3.3, -0.8)	0.002	906	-1.8 (-3.5, -0.0)	0.05	1206	-2.4 (-3.9, -0.9)	0.002
Non-Greek	563	8.8 (6.3, 11.4)	<.0001	243	13.2 (9.2, 17.4)	<.0001	123	6.7 (1.5, 12.2)	0.01	197	4.9 (0.9, 9.2)	0.02
Any*	4421	-0.8 (-1.6, -0.0)	0.05	1981	-0.3 (-1.5, 0.9)	0.61	1037	-0.8 (-2.4, 0.9)	0.36	1408	-1.5 (-2.9, 0.0)	0.04
Rural												
Greek	388	10.6 (7.6, 13.6)	0.002	108	24.1 (17.0, 31.5)	<.0001	93	12.7 (6.5, 19.2)	<0.0001	187	3.3 (-0.6, 7.4)	0.09
Non-Greek	38	14.0 (4.0, 24.9)	0.005	10	15.5 (-2.4, 36.8)	0.09	11	18.1 (0.3, 39.0)	0.05	17	4.9 (-7.6, 19.1)	0.46
Any*	427	10.9 (8.1, 13.9)	<.0001	118	24.3 (17.6, 31.4)	<.0001	104	14.7(8.6, 21.1)	<0.0001	205	3.0 (-0.7, 6.9)	0.11
HDI												
	PC			PC			PC			PC		
Greek		-8.6 (-14.8, -1.9)	0.01		-11.3 (-20.8, -1.4)	0.03		3.5 (-10.9, 20.1)	0.66		-12.3 (-22.2, -1.2)	0.03
Non-Greek		-5.7 (-25.0, 18.7)	0.62		-19.8 (-44.8, 16.6)	0.25		20.0 (-28.6, 101.7)	0.49		-1.3 (-30.7, 40.5)	0.94
All*		-9.5 (15.3, -3.2)	0.004		-14.0 (-22.3, -4.7)	0.004		3.3 (-10.4, 19.3)	0.65		-11.4 (-20.8, -0.7)	0.04

*including missing maternal nationality values

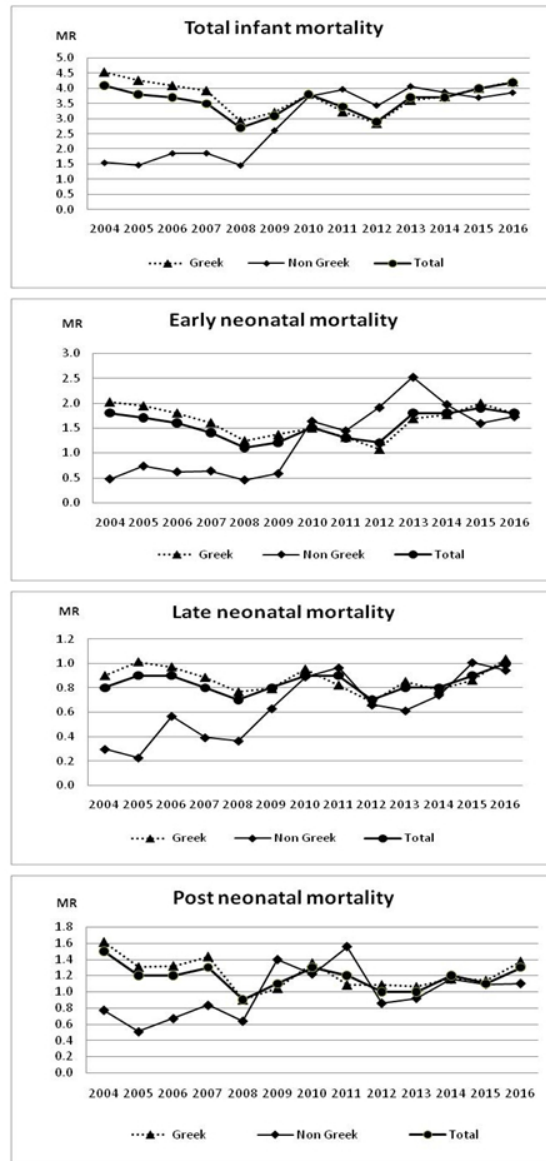
Table 3. Joinpoint regression derived Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant (IMR), early neonatal (ENMR), late neonatal (LNMR) and post neonatal (PNMR) mortality rates by maternal nationality.

	IMR				ENMR			
	Years	N	APC (95% CI)	p-value	Time period	N	APC (95% CI)	p-value
Greek	2004-12	2870	-4.5 (-7.6, -1.3)	0.01	2004-11	1118	-6.5 (-11.4, -1.4)	0.02
	2012-16	1368	9.3 (-1.1, 20.9)	0.07	2011-16	731	10.2 (-0.4, 21.9)	0.06
Non-Greek	2004-11	333	17.1 (8.1, 26.9)	0.002	2004-16	258	13.8 (6.7, 21.3)	0.001
	2011-16	282	0.2 (-11.5, 13.5)	0.97				
All*	2004-08	1807	-7.5 (-14.6, 0.3)	0.06	2004-08	780	-10.7 (-19.9, -0.5)	0.04
	2008-16	3055	3.6 (0.7, 6.6)	0.02	2008-16	1327	6.1 (2.1, 10.3)	0.01
	LNMR				PNMR			
	Years	N	APC (95% CI)	p-value	Time period	N	APC (95% CI)	p-value
Greek	2004-16	995	-0.6 (-2.5, 1.4)	0.54	2004-16	1393	-1.7 (-4.0, 0.8)	0.16
Non-Greek	2004-16	138	9.1 (3.5, 14.9)	0.003	2004-16	218	4.7 (-0.8, 10.6)	0.09
All*	2004-16	1136	0.6 (-1.3, 2.5)	0.48	2004-16	1617	-0.8 (-3.0, 1.4)	0.42

* Including missing maternal nationality values.

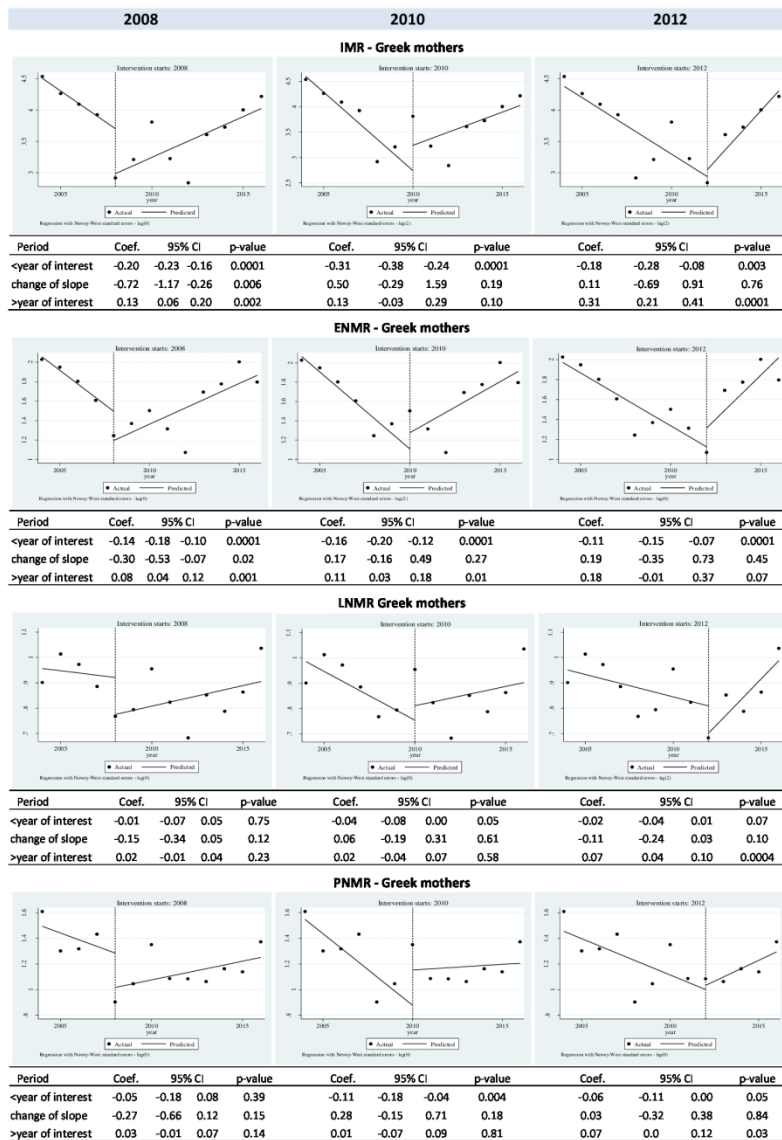
No break in the time period examined was identified for ENMR in non-Greeks, as well as for LNMR and PNMR measures in Greeks, non-Greeks or the total study population.

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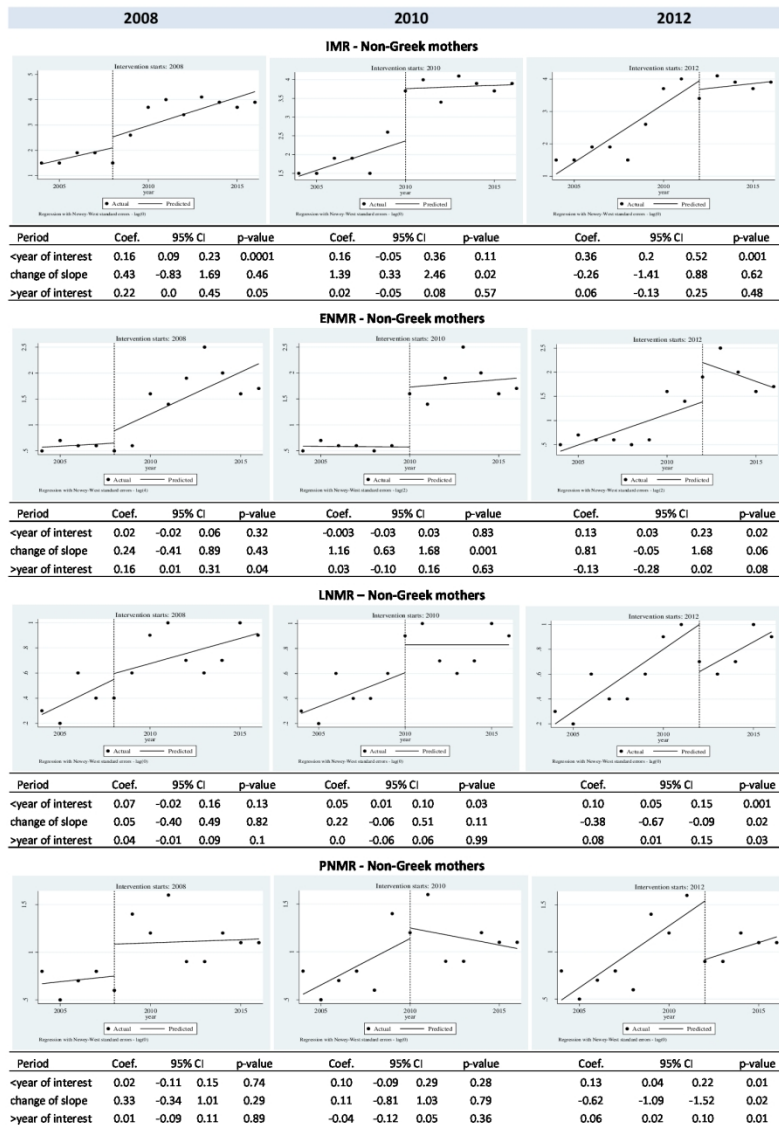
Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

60x81mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to Greek mothers.

140x198mm (300 x 300 DPI)



Interrupted Time Series analyses for evolution of infant (IMR), early (ENMR), late (LNMR) and post neonatal mortality rates (PNMR) in alternative prespecified years of interest (2008, 2010 and 2012) in infants born to non-Greek mothers.

140x198mm (300 x 300 DPI)

Suppl. Table 1. Infant deaths and total infant mortality rates (IMR) by place of residence (2004-2016).

Year	Infants born to mothers living in urban/semiurban areas		Infants born to mothers living in rural areas	
	Infant deaths (N)	Mortality rates/1000 livebirths	Infant deaths (N)	Mortality rates/1000 livebirths
2004	400	4.5	29	1.8
2005	383	4.2	26	1.6
2006	382	4.0	33	1.9
2007	377	3.9	20	1.2
2008	298	2.9	16	0.9
2009	344	3.4	27	1.5
2010	403	4.1	33	1.9
2011	326	3.5	31	2.2
2012	276	3.2	17	1.3
2013	334	4.2	11	0.8
2014	284	3.6	55	3.9
2015	299	3.8	61	4.5
2016	315	4.0	68	4.9

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Research checklist- STROBE Statement—checklist

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