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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

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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

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

CONCLUSIONS

HDI and rural residence were significant predictors of infant health. The strongly decreasing IMR -especially ENMR- trends among Greeks were stagnated after a lag time of ~four years of crisis approximating the previously sharply increasing trends among non-Greek infants.

Strengths of this study

- Longest follow-up period of national data, as contrasted to previously Greek-based studies.
- Moreover, maternal ethnicity is for first time considered in the analyses explaining part, if not most, of the heterogeneity of trends through the study period.
- Three complimentary statistical methodologies were used to describe the overall evolution of infant mortality and its components.

Limitations

- Absence of a linkage system between birth and death data.
- 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 disproportionally 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

proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016. Total health expenditures and government expenditure on health care were both decreased by 34% per capita over the period 2008-2016,[13,14] whereas unmet healthcare needs increased.[15] Besides, during the last years Greece experienced large refugee flows[16,17] with an anticipated negative impact on the country's economy and population health indicators. Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth and stillbirth rates, have been also observed;[18,19] however, sparse data exist regarding the potential association of the crisis with IMR. It has been initially reported that during the period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to the steady decrease observed during the preceding decade.[20,21] Ecological correlations may prone, however, to fallacies, whereas the different parts shaping the two main components of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly examined along with other factors possibly influencing the infants' health, especially socioeconomic status and access to health care delivery.

The aims of the current study were to explore time trends in early (<7 days of life) and late (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during the period 2004-2016 after taking into account nationality and place of residence, as well as changes in the Human Development Index (HDI) during the study period as a proxy of individual and collective measures of socioeconomic impact and health care access.

Materials and Methods

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

one, infant deaths; linkage of the two files was not possible as the personal identification number was not available in ELSTAT. Information on maternal demographic characteristics, such as nationality (available since 2004) and place of residence (available till 2014), as well as on the infants' age of death, were also provided.

Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of deaths over the number of livebirths per year. Annual percent of change (APC) during the study period were initially estimated through Poisson regression analysis using the underlying population of each set as an offset variable. Subsequently, data were stratified and analyzed by maternal nationality (Greek *vs.* non-Greek) and place of residence (Urban/Semi-urban *vs.* Rural). Joinpoint regression analysis was thereafter applied to automatically derive, through an algorithm, different segments in the mortality evolution curves overall, as well as those by maternal nationality and place of residence. Interrupted Time Series (ITS) analyses were also undertaken to explore the effect of crisis in alternative years, notably 2008 indicating the maximum value of the Gross Domestic Product of the country (Source: Aggregate National Accounts) considered to indicate the initiation of the crisis, as well as two subsequent years notably 2010 and 2012 to control for any time lags in observing the impact of the crisis. All ITS models were checked and appropriately adjusted for possible auto-correlation.

Human development index (HDI) is a summary measure of average achievements of a country's population in three areas including life expectancy, education and *per capita* income indicators. Annual HDI values for the underlying populations in the year of death were extracted from the United Nations Development Program website (http://hdr.undp.org/en/composite/HDI), whereas Poisson regression analysis was used to explore the association of one standard deviation of HDI with total IM and its components.

All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Ethical approval: Not required.

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 infants born to Greek mothers. 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. The corresponding figures for the early, late and post neonatal period were 1.5‰, 0.8‰ and 1.2‰ respectively. 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).

Overall, during the study-period, among infants born to Greek mothers, IMR, particularly PNMR, declined significantly (-0.9% and -1.6% annually, respectively, p=0.02 for each), albeit differentially by place of residence (Table 1); significant decline of IMR trends (-3.5% annually, p<0.0001) and all its components was observed among infants born to Greek mothers living in urban areas (maximum decrease in ENMR: -4.1% annually, p<0.0001) whereas, among infants born to Greek mothers in rural areas, a significant increase of IMR trend was observed (+5.2% annually, p=0.01) resulting mainly from increased ENMR (+24.1% annually, p<0.0001). By contrast, among infants of non-Greek mothers, the low starting IMR increased significantly by +9.4% annually (p<0.0001), due to significant increases of ENMR, LNMR and PNMR (max ENMR: +12.5% annually, p<0.0001) leading to an erroneously non-significant pattern of IMR evolution for Greece overall (p=0.50). The inverse associations of HDI with IMR, ENMR and PNMR were restricted to Greek mothers' infants (Table 1).

Results of joinpoint regression analyses were similar to those derived by the Poisson regression apart from models displayed in Table 2 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% annually, p=0.01); this was mainly due to a significant decline in ENMR trend till 2011 (-6.5% annually, p=0.02). Of note, however, in the most recent study period (2012-2016) sizeable, borderline significant increases of IMR (+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% annually, p=0.002) were restricted to the period 2004-2011 with no fluctuation thereafter; finally, IMR approximated those of Greek mothers' infants.

ITS analyses in the preset years 2008, 2010 and 2012 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, observed essentially before the crisis, 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 borderline increases of ~10% annually, thereafter, in IMR and ENMR trends among infants born to Greek mothers. Changes in HDI during the study period were also reflected in the inverse associations of ENMR and IMR, but also PNMR, among infants born to Greek mothers.

Strengths of the present investigation, as contrasted to previously greek-based published studies,[9,18,20,21,22] include the longest follow-up period of national data, namely since 2004, before the crisis, when the first data on maternal ethnicity became electronically available, to the latest available year 2016. Of great importance is also the fact that, for the first time, the maternal ethnicity was considered in the analyses explaining part, if not most, of the heterogeneity of trends through the study period. To this end, three complimentary statistical methodologies were used to describe the overall evolution depicted in Figure 1. Thus, we were able to enhance the validity of the results pertaining to the study of the evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which individual data have been available on a nationwide level among both deaths and livebirths during the study period. Calculation of IMR and its components was based on the number of livebirths; yet, the absence of a linkage system between birth and death data, as well as other official registries in Greece, has not allowed use of known determinants of socioeconomic deprivation or social coherence, such as parental education, employment/occupation marital status, family income and household size. Neither were data on the role of biological factors, such as parental age, gestational age and birthweight or multiplicity of pregnancy available for both the livebirths and deaths series.[5,19,23] Lastly, analyses by specific cause of infant death were not set among outcome measures of this study.

Assessing migration as a determinant of perinatal health outcome and infant death in the developed countries is a complex undertaking resulting in conflicting results of published studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor for unfavorable perinatal outcomes and increased neonatal and infant mortality,[18,24-31] especially if it coincides with a financial crisis, as was the cases in Greece. Factors possibly contributing to the increased risk for poorer outcomes among children born to migrants include socioeconomic disadvantage, poor communication, discrimination, reduced utilization of health facilities, low quality of care, but also stress and consanguinity or differing attitudes to screening and termination of pregnancy associated with preterm birth, low birth weight or congenital anomalies and lethal inherited diseases.[24,28,32-34] By contrast, other studies present similar or even better perinatal health outcomes among some migrant groups than among natives ("healthy migrant effect/paradox").[24-26,35,36] Refugees have been recognized as the most vulnerable group suffering increased severe neonatal morbidity and infant mortality risk,[24,26] although no absolutely clear pattern regarding refugee or non-refugee status among migrants has been identified.[32]

In our study, starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers. The numbers by individual maternal nationality were, however, small to explore the tentative influence of the changing maternal nationality case mix during the study period. Of note, the ratio of non-Greek infants among live births during 2009-2016 *vs.* 2004-2008 was only 1.32, whereas the respective figure among infant deaths was almost 3-fold (data not shown). Indeed, a considerable proportion of non-Greek pregnant women before the crisis were serving as home-aids in relatively affluent Greek families, as contrasted to the adverse conditions envisaged by pregnant women and their offspring during the most recent massive migration movements from deprived countries to European Union member states via Greece which coincided with the crisis in our country. Actually, in the pre-crisis era non-Greek mothers of newborn comprised mainly economic migrants, most of them of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece experienced an unprecedented influx of refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.[16,17]

The strongly decreasing IMR, especially ENMR, trends among Greek infants were stagnated after a lag time of ~four years of crisis and equalized with the previously sharply increasing trends among non-Greek maternal nationality infants; this time lag is reasonable[37] and in line with previous findings showing that following reductions in the government healthcare spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4 and 5 years later, respectively.[6] The irony is that the period 2012-2016, during which the crisis was deepening[13,14] and stricter economic austerity measures were applied,[38] disparities gap in IMR trends diminished against the Greek population; IMR trends deteriorated only in infants born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends approached an anelastic highest value up to 2011 with no fluctuation thereafter.

Disparities in IMR still exist across geographic areas even in well developed countries; i.e. IMR in the United States vary by urbanization level of maternal residency being lowest in large urban counties but highest in rural areas.[39] Rural women may face health challenges related to geographic barriers to care (less timely and/or appropriate care) and physician shortages, but they may also present differences in a number of socioeconomic and demographic risk factors, such as less education, lower income, younger age at pregnancy, or greater number of children, in comparison with their urban counterparts.[40,41] Disparities in IMR trends between urban/semi urban and rural areas in Greece would not be surprising if changes in IMR trends were observed in the same direction; the increasing IMR trends during the study period in infants born to Greek mothers living in rural areas, as opposed to the declining IMR trends in those born to Greek mothers living in urban/semi urban areas, is worrisome; specific causes should be further studied and addressed. The increasing IMR trends in infants born to non-Greek mothers despite living in urban areas can be explained by previous reports showing that other risk factors, i.e. young maternal age (<20 years) or maternal ethnic minority, may be more powerful than place of residence.[41]

As expected, among the three IMR components, ENMR was the most "sensitive" in reflecting adverse impacts on child health as further reflected in the IMR trends. Specifically, ENMR was overall positively associated with rural place of residence of Greek children, notably before the "break" of 2012, with the increased ENMR neutralizing the urbanization differentials among newborn of Greek mothers. ENMR in developed countries, including Greece. represents more than 70% of infant deaths on account mainly of prematurity/low birth weight and congenital anomalies.[14,42-45] Actually, it reflects perinatal health and care during pregnancy and labor, and also postnatal care in the first week of life.[44] Increased incidence of impaired perinatal parameters including low birth weight, prematurity, increased maternal age and rate of caesarian section, and also increased stillbirth rate in Greek women younger than 25 years of age, has been reported during the years of the economic decline in Greece.[18,19] Cuts in public health expenditures between 2008 and 2016, reduction in health care workforce and pediatric nurses, as well as reduction in the number of obstetrics beds, obstetricians and midwifes (-45.5%, -60.2% and -27.5%, respectively)[14] could possibly explain, at least in part, the observed increases in ENMR trends during the study period in Greece.

The exact mechanisms leading to the disparities in trends of neonatal and infant mortality observed in this study remain to be further explored. Specific maternal, family and infant features, including detailed and punctual information on the causes of infant deaths, would have shed more light on the links between IMR trends and socioeconomic factors but were beyond the scope of this article and left for future research. Meanwhile, policies and programs should be implemented to mitigate the negative impact of the crisis on population and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of low income, or rural place of residence, should be specifically addressed and their rights to health protected. Strong governmental integration policy for minorities paired with initiatives to improve social coherence, a deeply rooted mechanism for protection of health among those in need in the Greek society, along with improvements in primary health care delivery could help to alleviate the cost in infant lives and ensure healthy adulthood.[30,45] Irrespective of the crisis, improvements in the quality of perinatal care, such as centralization of very preterm deliveries, establishment of regional perinatal centers, and monitoring of the implementation of evidence-based practices, could decrease ENMR and improve the perinatal indicators.[44]

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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); Percept of Change (PC) for 1 Standard Deviation of Human Development Index (HDI, 2000-2015) controlling for year.

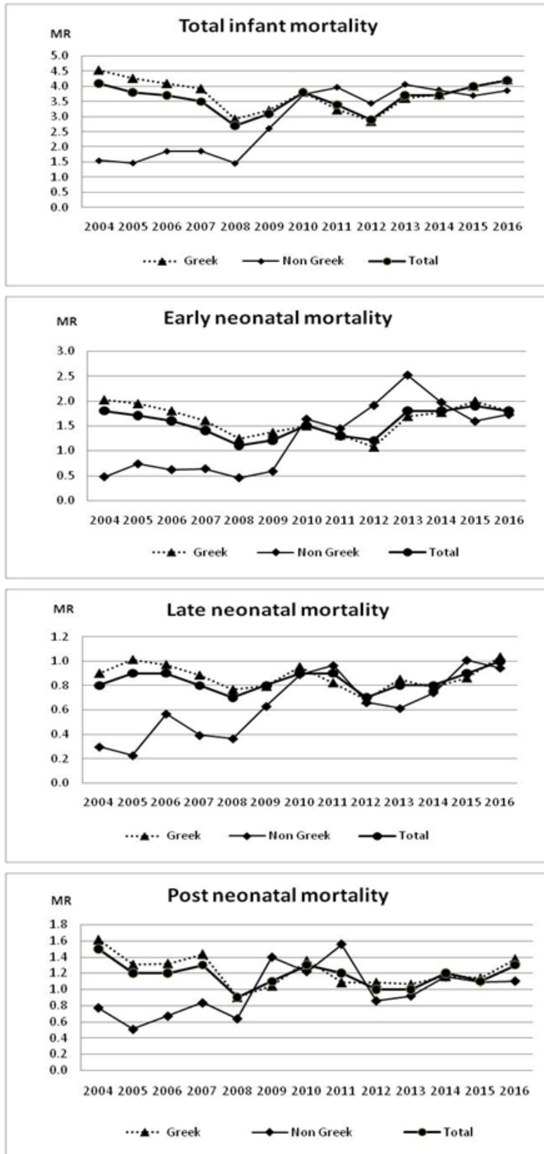
Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	**-0.9 (-1.7,-0.1)**	**0.02**	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	**-1.6 (-3.0,-0.2)**	**0.02**
Non-Greek	615	**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

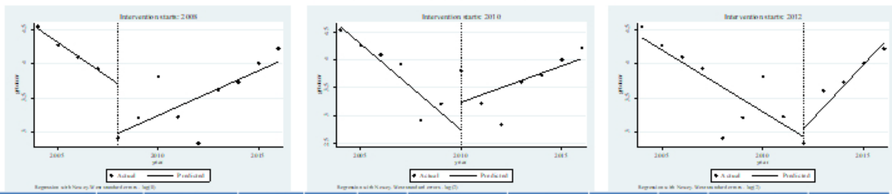


Infant, Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

190x254mm (96 x 96 DPI)

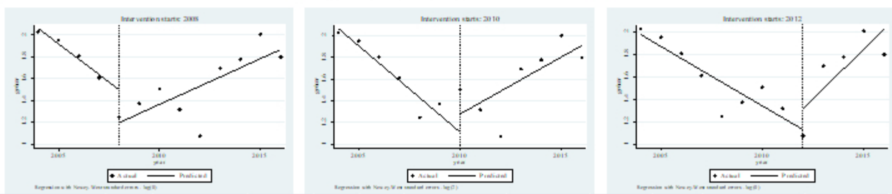
2008 | 2010 | 2012

IMR - Greek mothers



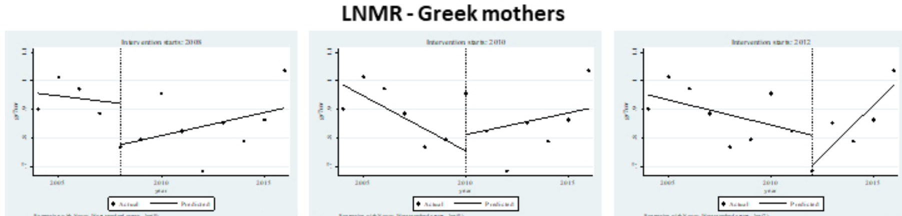
Period	coef	95% CI		p-value		coef	95% CI		p-value		coef	95% CI		p-value
<year of interest	-0.20	-0.23	-0.16	0.0001		-0.31	-0.38	-0.24	0.0001		-0.18	-0.28	-0.08	0.003
>year of interest	0.13	0.06	0.20	0.002		0.13	-0.03	0.29	0.10		0.31	0.21	0.41	0.0001

ENMR - Greek mothers



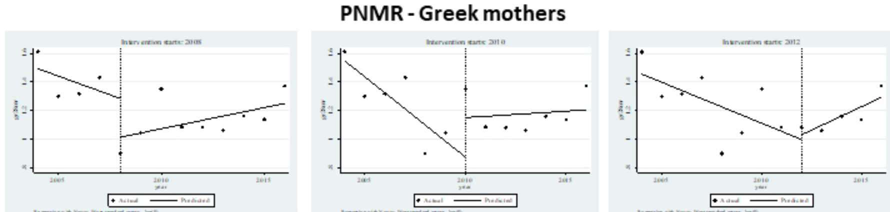
Period	coef	95% CI		p-value		coef	95% CI		p-value		coef	95% CI		p-value
<year of interest	-0.14	-0.18	-0.10	0.0001		-0.16	-0.2	-0.12	0.0001		-0.11	-0.15	-0.07	0.0001
>year of interest	0.08	0.04	0.12	0.001		0.11	0.03	0.18	0.01		0.18	-0.01	0.37	0.07

LNMR - Greek mothers



Period	coef	95% CI		p-value		coef	95% CI		p-value		coef	95% CI		p-value
<year of interest	-0.01	-0.07	0.05	0.75		-0.04	-0.08	0.00	0.05		-0.02	-0.04	0.01	0.07
>year of interest	0.02	-0.01	0.04	0.23		0.02	-0.04	0.07	0.58		0.07	0.04	0.1	0.0004

PNMR - Greek mothers



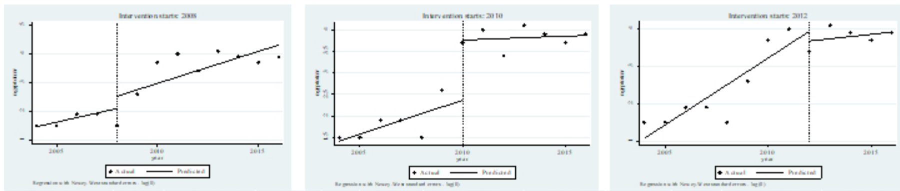
Period	coef	95% CI		p-value		coef	95% CI		p-value		coef	95% CI		p-value
<year of interest	-0.05	-0.18	0.08	0.39		-0.11	-0.18	-0.04	0.004		-0.06	-0.11	0.00	0.05
>year of interest	0.03	-0.01	0.07	0.14		0.01	-0.07	0.09	0.81		0.07	0	0.12	0.03

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

190x254mm (96 x 96 DPI)

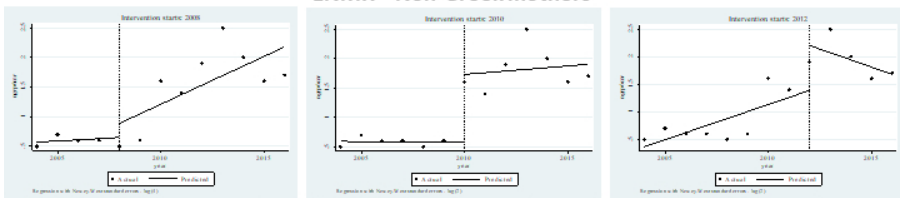
2008 2010 2012

IMR – Non-Greek mothers



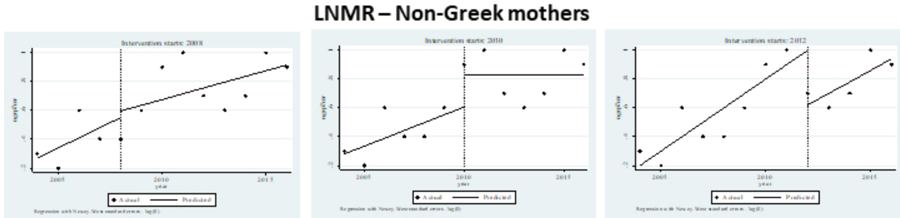
Period	coef	95% CI		p-value	coef	95% CI		p-value	coef	95% CI		p-value
<year of interest	0.16	0.09	0.23	0.0001	0.16	-0.05	0.36	0.11	0.36	0.2	0.52	0.001
>year of interest	0.22	0	0.45	0.05	0.02	-0.05	0.08	0.57	0.06	-0.13	0.25	0.48

ENMR – Non-Greek mothers



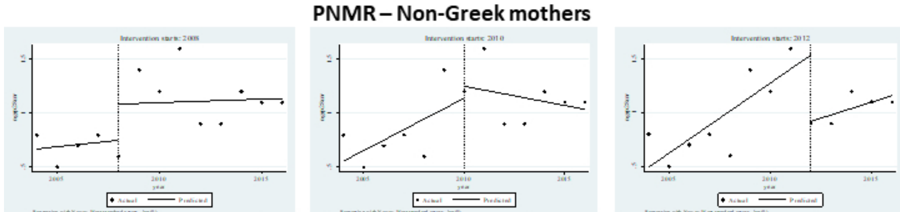
Period	coef	95% CI		p-value	coef	95% CI		p-value	coef	95% CI		p-value
<year of interest	0.02	-0.02	0.06	0.32	-0.003	-0.03	0.03	0.83	0.13	0.03	0.23	0.02
>year of interest	0.16	0.01	0.31	0.04	0.03	-0.10	0.16	0.63	-0.13	-0.28	0.02	0.08

LNMR – Non-Greek mothers



Period	coef	95% CI		p-value	coef	95% CI		p-value	coef	95% CI		p-value
<year of interest	0.07	-0.02	0.16	0.13	0.05	0.01	0.10	0.03	0.10	0.05	0.15	0.001
>year of interest	0.04	-0.01	0.09	0.1	0.0	-0.06	0.06	0.99	0.08	0.01	0.15	0.03

PNMR – Non-Greek mothers



Period	coef	95% CI		p-value	coef	95% CI		p-value	coef	95% CI		p-value
<year of interest	0.02	-0.11	0.15	0.74	0.1	-0.09	0.29	0.28	0.13	0.04	0.22	0.01
>year of interest	0.01	-0.09	0.11	0.89	-0.04	-0.12	0.05	0.36	0.06	0.02	0.1	0.01

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 Non-Greek mothers.

190x254mm (96 x 96 DPI)

Research checklist- STROBE Statement—checklist

	Item No	Page number
Title and abstract	1	1
		3
Introduction		
Background/rationale	2	6-7
Objectives	3	7
Methods		
Study design	4	7-8
Setting	5	7-8
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

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

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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

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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

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

CONCLUSIONS

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

Strengths of this study

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

Limitations

- Absence of a linkage system between birth and death data.

- 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 disproportionally 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 proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016. Total health expenditures and government expenditure on health care were both decreased by 34% per capita over the period 2008-2016,[13,14] whereas unmet healthcare needs increased.[15] Besides, during the last years, Greece experienced large refugee flows[16,17] with an anticipated negative impact on the country's economy and population health indicators. Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth and stillbirth rates, have been also observed;[18,19] however, sparse data exist regarding the potential association of the crisis with IMR. It has been initially reported that during the period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to the steady decrease observed during the preceding decade.[20,21] Ecological correlations may prone, however, to fallacies, whereas the different parts shaping the two main components of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly examined along with other factors possibly influencing the infants' health, especially socioeconomic status and access to health care delivery.

The aims of the current study were to explore time trends in early (<7 days of life) and late (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during the period 2004-2016 after taking into account nationality and place of residence, as well as changes in the Human Development Index (HDI) during the study period as a proxy of individual and collective measures of socioeconomic impact and health care access.

Materials and Methods

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

Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of deaths over the number of livebirths per year. Annual percent of change (APC) during the study period was initially estimated through Poisson regression analysis using the underlying population of each set as an offset variable. Subsequently, data were stratified and analyzed by maternal nationality (Greek *vs.* non-Greek) and place of residence (Urban/Semi-urban *vs.* Rural). Joinpoint regression analysis[22] was thereafter applied to automatically derive, through an algorithm, different segments in the mortality evolution curves overall, as well as those by maternal nationality and place of residence. Interrupted Time Series (ITS) analyses were also undertaken as a sensitivity analysis to further explore the effect of crisis on IMR and its components in alternative prespecified years, notably 2008, considered to indicate the initiation of the crisis in Greece as the value of the Gross Domestic Product of the country was maximum at that year but dropped afterwards (Source: Aggregate National Accounts), and in two successive periods two years apart (2010 and 2012), to control for possible time lags in observing the impact of the crisis. All ITS models were verified and appropriately adjusted for possible auto-correlation; autoregressive integrated moving-average models were used to control for autocorrelation and to estimate treatment effects over multiple periods. In our ITS analysis a slope "<year of interest" is fitted until the introduction of the crisis, ">year of interest" represents the change in the level of the mortality immediately following the initiation of the crisis and "change of slope" represents the differences between pre and post crisis intervention slopes.

Human development index (HDI) is a summary measure of average achievements of a country's population in three areas including life expectancy, education and *per capita* income indicators. Annual HDI values for the underlying populations in the year of death were extracted from the United Nations Development Program website (http://hdr.undp.org/en/composite/HDI), whereas Poisson regression analysis was used to explore the association of one standard deviation of HDI with total IM and its components. All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Ethical approval: Not required.

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).

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

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

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% annually, p=0.01); this was mainly due to a significant decline in ENMR trend till 2011 (-6.5% annually, p=0.02). Of note, however, in the most recent study period (2012-2016) sizeable, borderline significant, increases of IMR (+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% 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 borderline increases of ~10% annually, thereafter, in IMR and ENMR trends among infants born to Greek mothers. Changes in HDI during the study period were also reflected in the inverse associations of HDI with ENMR and IMR, but also PNMR, among infants born to Greek mothers.

Strengths of the present investigation, as contrasted to previously Greek-based published studies,[9,18,20,21,23] include the longest follow-up period of national data, namely since 2004, before the crisis, when the first data on maternal ethnicity became electronically available, to the latest available year 2016. Of great importance is also the fact that, for the first time, the maternal ethnicity was considered in the analyses explaining part, if not most, of the heterogeneity of trends through the study period. To this end, three complimentary statistical methodologies were used to describe the overall evolution depicted in Figure 1. Thus, we were able to enhance the validity of the results pertaining to the study of the evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which individual data have been available on a nationwide level among both deaths and livebirths during the study period. Calculation of IMR and its components was based on the number of livebirths; yet, the absence of a linkage system between birth and death data, as well as other official registries in Greece, has not allowed use of known determinants of socioeconomic deprivation or social coherence, such as parental education, employment/occupation, marital status, family income and household size. Neither were data on the role of biological factors, such as parental age, gestational age and birthweight or multiplicity of pregnancy available for both the livebirths and deaths series.[5,19,24] Besides, the study period, with available information on maternal nationality and place of residence, was rather short leading to ITS analyses with few data points; ITS analysis can be used even for few observations; no log-transformation is needed but the results should be interpreted with caution as the power depends on various factors.[25] Lastly, analyses by specific cause of infant death were not set among the outcome measures of this study.

Assessing migration as a determinant of perinatal health outcome and infant death in the developed countries is a complex undertaking resulting in conflicting results of published studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor for unfavorable perinatal outcomes and increased neonatal and infant mortality,[18,26-33] especially if it coincides with a financial crisis, as was the case in Greece. Factors possibly contributing to the increased risk for poorer outcomes among children born to migrants include socioeconomic disadvantage, poor communication, discrimination, reduced utilization of health facilities, low quality of care, but also stress and consanguinity or differing attitudes to screening and termination of pregnancy associated with preterm birth, low birth weight or congenital anomalies and lethal inherited diseases.[26,30,34-36] By contrast, other studies present similar or even better perinatal health outcomes among some migrant groups than among natives ("healthy migrant effect/paradox").[26-28,37,38] Refugees have been recognized as the most vulnerable group suffering increased severe neonatal morbidity and infant mortality risk,[26,28] although no absolutely clear pattern regarding refugee or non-refugee status among migrants has been identified.[34]

In our study, starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers. The numbers by individual maternal nationality were, however, small to explore the tentative influence of the changing maternal nationality case mix during the study period; this issue needs to be further followed-up by other types of research methodology. Of note, the ratio of non-Greek infants among live births during 2009-2016 *vs.* 2004-2008 was only 1.32, whereas the respective figure among infant deaths was almost 3-fold (data not shown). Indeed, a considerable proportion of non-Greek pregnant women before the crisis were serving as home-aids in relatively affluent Greek families, as contrasted to the adverse conditions envisaged by pregnant women and their offspring during the most recent massive migration movements from deprived countries to European Union member states via Greece which coincided with the crisis in our country. Actually, in the pre-crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most of them of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece experienced an influx of refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.[16,17] It could be suggested that changes in the homogeneity of foreign mothers during the study period, in association with the country's economic difficulties, might have led from the "healthy migrant effect", observed before 2008, to the deterioration of IM indicators and IMR trends, afterwards, in infants born to non-Greek mothers.

Simultaneously with immigration to/through Greece, the country experienced the third wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left Greece since the onset of the economic crisis, in 2008, seeking new opportunities and employment in other countries, mainly Germany, the United Kingdom and the Netherlands.[39,40] The current emigration wave of Greeks involved mostly highly-educated people (the so called "brain-drain") of young age, leading to a decrease in the number of Greek women of childbearing age.[41] This fact, along with the decrease in the fertility rate by almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual number of livebirths in Greece by almost 23% during the period of the economic crisis.[41,42] Furthermore, the flow of mostly affluent and well educated people going outside Greece might have also contributed, to a certain extent, to the observed increases in IMR among Greek children following the crisis.

The strongly decreasing IMR, especially ENMR, trends among Greek infants were stagnated after a lag time of ~four years of crisis and equalized with the previously sharply increasing trends among non-Greek maternal nationality infants; this time lag is reasonable[43] and in line with previous findings showing that following reductions in the government healthcare spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4 and 5 years later, respectively.[6] The irony is that the period 2012-2016, during which the crisis was deepening[13,14] and stricter economic austerity measures were applied,[44] disparities gap in

IMR trends diminished against the Greek population; IMR trends deteriorated only in infants born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends approached an anelastic highest value up to 2011 with no fluctuation thereafter. The importance of two sub-analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized; when trends in the entire study population were assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of previous relevant studies in Greece which did not take into consideration the maternal nationality.[20]

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

As expected, among the three IMR components, ENMR was the most "sensitive" in reflecting adverse impacts on child health as further reflected in the IMR trends. Specifically, ENMR was overall positively associated with rural place of residence of Greek children, notably before the "break" of 2012, with the increased ENMR neutralizing the urbanization differentials among newborns of Greek mothers. ENMR, in developed countries, including Greece, represents more than 70% of neonatal deaths on account mainly of prematurity/low birth weight and congenital anomalies.[14,48-51] Actually, it reflects perinatal health and care during pregnancy and labor, and also postnatal care in the first week of life.[50] Increased incidence of impaired perinatal parameters including low birth weight, prematurity, and increased maternal age and rate of caesarian section, have been reported during the years of the economic decline in Greece.[18,19] Cuts in public health expenditures between 2008 and 2016, reduction in health care workforce and pediatric nurses, as well as reduction in the number of obstetrics beds, obstetricians and midwifes (-45.5%, -60.2% and -27.5%, respectively)[14] could possibly explain, at least in part, the observed increases in ENMR trends during the study period in Greece. Besides, it is worth mentioning that IMR and ENMR are influenced by variation in the registration of births in case of uncertain viability.[52] In Greece, like in other countries,[53] misclassification in reporting of extremely preterm births of <24 weeks of gestation, as live or stillborn, may exist. Further analysis of IMR trends after excluding extremely preterm births would be useful to minimize any registration variation; however, as mentioned in the limitations of this study, gestational age data of the study population are missing. To clarify this issue we analyzed separately the infant deaths in the first day of life; trends of IMR in this age group, over the study period, were non-significant (average annual percent change: -1.22%; 95% CI: -3.79% to 1.42%; p=0.36).

The exact mechanisms leading to the disparities in trends of neonatal and infant mortality observed in this study remain to be further explored. Specific maternal, family and infant features, including detailed and punctual information on the causes of infant deaths, would have shed more light on the links between IMR trends and socioeconomic factors but were beyond the scope of this article and left for future research. Meanwhile, policies and programs should be implemented to mitigate the negative impact of the crisis on population and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of low income, or rural place of residence, should be specifically addressed and their rights to health protected. Barriers in the access of refugees to the Greek health care system have been mostly related to language, culture, and inadequate information about the healthcare system, but also include difficulties in the coordination of Health Services, transportation problems, issues in obtaining expertise medical assessment in the camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for health and social care services, and administrative barriers, among others.[54] In response, the Greek government and several Non-Governmental Organizations initiated commendable actions, i.e. National Health System services free of charge for uninsured and vulnerable social groups including asylum seekers , translation services in public hospitals, access to specialist care/treatment with Gynecologists (mostly women), midwives, dentists, psychologists, and psychiatrists being lately included in the camp clinics;[54] these actions may have prevented deterioration of IMR which are being kept at steady levels after 2011 in infants of non-Greek mothers; efforts should be continued and intensified, however, as to ensure equity with local populations. Strong governmental integration policy for minorities paired with initiatives to improve social coherence, a deeply rooted mechanism for protection of health among those in need in the Greek society, along with further improvements in primary health care delivery could help to alleviate the cost in infant lives and ensure healthy adulthood.[32,51] Irrespective of the crisis, improvements in the quality of perinatal and neonatal care, including centralization of very preterm deliveries, establishment of regional perinatal centers, monitoring of the implementation of evidence-based practices in maternity and neonatal units, as well as increase in health expenditures, health care workforce, number of doctors and midwifes/nurses, could decrease ENMR, eventually leading to overall decrease in IMR in Greece.[50]

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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

	Infants born to Greek mothers			Infants born to non-Greek mothers		
Year	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.

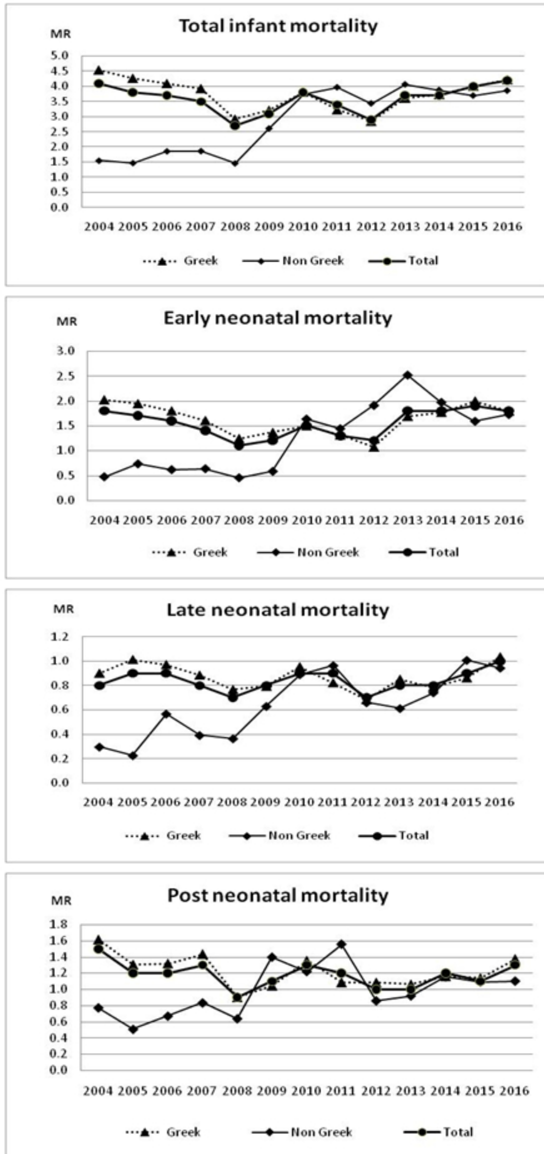
Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	**-0.9 (-1.7,-0.1)**	**0.02**	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	**-1.6 (-3.0,-0.2)**	**0.02**
Non-Greek	615	**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



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

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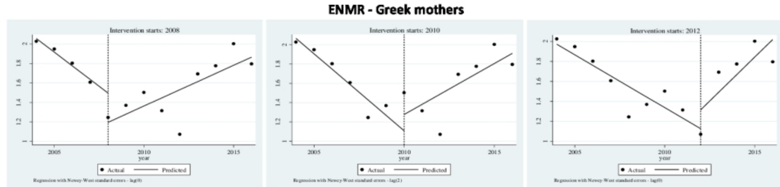
2008	2010	2012

IMR - Greek mothers

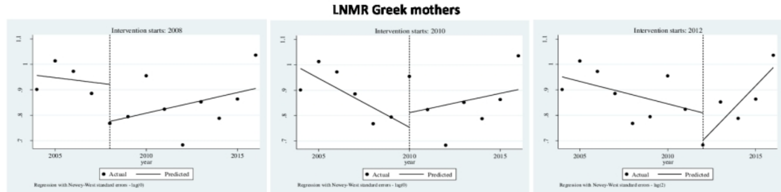
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.20	-0.23	-0.16	0.0001	-0.31	-0.38	-0.24	0.0001	-0.18	-0.28	-0.08	0.003
change of slope	-0.72	-1.17	-0.26	0.006	0.50	-0.29	1.59	0.19	0.11	-0.69	0.91	0.76
>year of interest	0.13	0.06	0.20	0.002	0.13	-0.03	0.29	0.10	0.31	0.21	0.41	0.0001

ENMR - Greek mothers



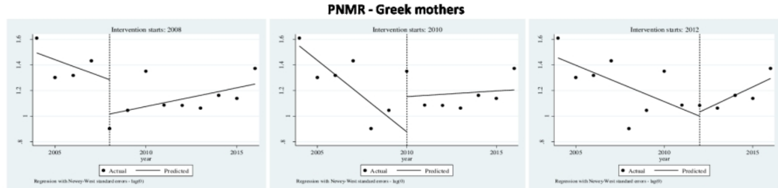
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.14	-0.18	-0.10	0.0001	-0.16	-0.20	-0.12	0.0001	-0.11	-0.15	-0.07	0.0001
change of slope	-0.30	-0.53	-0.07	0.02	0.17	-0.16	0.49	0.27	0.19	-0.35	0.73	0.45
>year of interest	0.08	0.04	0.12	0.001	0.11	0.03	0.18	0.01	0.18	-0.01	0.37	0.07

LNMR Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.01	-0.07	0.05	0.75	-0.04	-0.08	0.00	0.05	-0.02	-0.04	0.01	0.07
change of slope	-0.15	-0.34	0.05	0.12	0.06	-0.19	0.31	0.61	-0.11	-0.24	0.03	0.10
>year of interest	0.02	-0.01	0.04	0.23	0.02	-0.04	0.07	0.58	0.07	0.04	0.10	0.0004

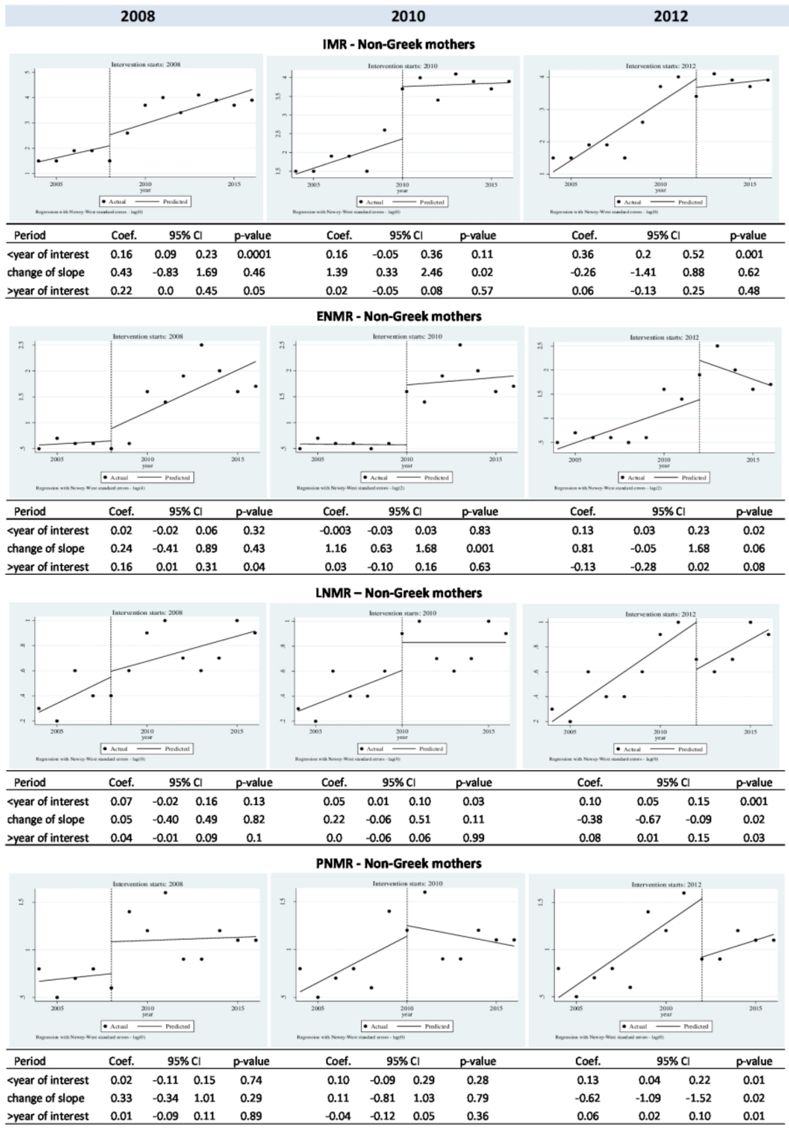
PNMR - Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.05	-0.18	0.08	0.39	-0.11	-0.18	-0.04	0.004	-0.06	-0.11	0.00	0.05
change of slope	-0.27	-0.66	0.12	0.15	0.28	-0.15	0.71	0.18	0.03	-0.32	0.38	0.84
>year of interest	0.03	-0.01	0.07	0.14	0.01	-0.07	0.09	0.81	0.07	0.0	0.12	0.03

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)



IMR - Non-Greek mothers

Period	2008 Coef.	2008 95% CI		2008 p-value	2010 Coef.	2010 95% CI		2010 p-value	2012 Coef.	2012 95% CI		2012 p-value
<year of interest	0.16	0.09	0.23	0.0001	0.16	-0.05	0.36	0.11	0.36	0.2	0.52	0.001
change of slope	0.43	-0.83	1.69	0.46	1.39	0.33	2.46	0.02	-0.26	-1.41	0.88	0.62
>year of interest	0.22	0.0	0.45	0.05	0.02	-0.05	0.08	0.57	0.06	-0.13	0.25	0.48

ENMR - Non-Greek mothers

Period	2008 Coef.	2008 95% CI		2008 p-value	2010 Coef.	2010 95% CI		2010 p-value	2012 Coef.	2012 95% CI		2012 p-value
<year of interest	0.02	-0.02	0.06	0.32	-0.003	-0.03	0.03	0.83	0.13	0.03	0.23	0.02
change of slope	0.24	-0.41	0.89	0.43	1.16	0.63	1.68	0.001	0.81	-0.05	1.68	0.06
>year of interest	0.16	0.01	0.31	0.04	0.03	-0.10	0.16	0.63	-0.13	-0.28	0.02	0.08

LNMR – Non-Greek mothers

Period	2008 Coef.	2008 95% CI		2008 p-value	2010 Coef.	2010 95% CI		2010 p-value	2012 Coef.	2012 95% CI		2012 p-value
<year of interest	0.07	-0.02	0.16	0.13	0.05	0.01	0.10	0.03	0.10	0.05	0.15	0.001
change of slope	0.05	-0.40	0.49	0.82	0.22	-0.06	0.51	0.11	-0.38	-0.67	-0.09	0.02
>year of interest	0.04	-0.01	0.09	0.1	0.0	-0.06	0.06	0.99	0.08	0.01	0.15	0.03

PNMR - Non-Greek mothers

Period	2008 Coef.	2008 95% CI		2008 p-value	2010 Coef.	2010 95% CI		2010 p-value	2012 Coef.	2012 95% CI		2012 p-value
<year of interest	0.02	-0.11	0.15	0.74	0.10	-0.09	0.29	0.28	0.13	0.04	0.22	0.01
change of slope	0.33	-0.34	1.01	0.29	0.11	-0.81	1.03	0.79	-0.62	-1.09	-1.52	0.02
>year of interest	0.01	-0.09	0.11	0.89	-0.04	-0.12	0.05	0.36	0.06	0.02	0.10	0.01

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

	Item No	Page number
Title and abstract	1	1
		3
Introduction		
Background/rationale	2	6-7
Objectives	3	7
Methods		
Study design	4	7-9
Setting	5	7
Participants	6	7-8
Variables	7	7-9
Data sources/ measurement	8*	*7-9*
Bias	9	N/A
Study size	10	N/A
Quantitative variables	11	7-9
Statistical methods	12	8-9
Results		
Participants	13*	9-10
Descriptive data	14*	9-10
Outcome data	15*	9-11
Main results	16	9-11
Other analyses	17	N/A
Discussion		
Key results	18	12
Limitations	19	12-13
Interpretation	20	13-18
Generalisability	21	17-18
Other information		
Funding	22	25

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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

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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

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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

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

CONCLUSIONS

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

Strengths of this study

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

Limitations

- Absence of a linkage system between birth and death data.
- 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 disproportionally 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

proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016. Total health expenditures and government expenditure on health care were both decreased by 34% per capita over the period 2008-2016,[13,14] whereas unmet healthcare needs increased.[15] Besides, during the last years, Greece experienced large refugee flows[16,17] with an anticipated negative impact on the country's economy and population health indicators. Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth and stillbirth rates, have been also observed;[18,19] however, sparse data exist regarding the potential association of the crisis with IMR. It has been initially reported that during the period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to the steady decrease observed during the preceding decade.[20,21] Ecological correlations may prone, however, to fallacies, whereas the different parts shaping the two main components of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly examined along with other factors possibly influencing the infants' health, especially socioeconomic status and access to health care delivery.

The aims of the current study were to explore time trends in early (<7 days of life) and late (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during the period 2004-2016 after taking into account nationality and place of residence, as well as changes in the Human Development Index (HDI) during the study period as a proxy of individual and collective measures of socioeconomic impact and health care access.

Materials and Methods

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

one, infant deaths; linkage of the two files was not possible as the personal identification number was not available in ELSTAT. Information on maternal demographic characteristics, such as nationality (available for years 2004-2016) and place of residence (available for years 2004-2014), as well as on the infants' age at death, were also provided.

Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of deaths over the number of livebirths per year. Annual percent of change (APC) during the study period was initially estimated through univariate Poisson regression analysis using the underlying population of each set as an offset variable. Subsequently, data were stratified and analyzed by maternal nationality (Greek *vs.* non-Greek) and place of residence (Urban/Semi-urban *vs.* Rural). Joinpoint regression analysis[22] was thereafter applied to automatically derive, by a software program, different segments in the mortality evolution curves overall, as well as those by maternal nationality and place of residence; the Joinpoint regression analysis is usually applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. Interrupted Time Series (ITS) analyses were also undertaken as a sensitivity analysis to further explore the effect of crisis on IMR and its components in alternative prespecified years, notably 2008, considered to indicate the initiation of the crisis in Greece -as the value of the Gross Domestic Product of the country was maximum at that year but dropped afterwards (Source: Aggregate National Accounts)-, and in two successive periods two years apart (2010 and 2012), to control for possible time lags in observing the impact of the crisis. All ITS models were verified and appropriately adjusted for possible auto-correlation; autoregressive integrated moving-average models were used to control for autocorrelation and to estimate treatment effects over multiple periods. In our ITS analysis a slope "<year of interest" is fitted until the introduction of the crisis, ">year of interest" represents the change in the level of the mortality immediately following the initiation of the crisis and "change of slope" represents the differences between pre and post crisis intervention slopes.

Human development index (HDI) is a summary measure of average achievements of a country's population in three areas including life expectancy, education and *per capita* income indicators. Annual HDI values for the underlying populations in the year of death were extracted from the United Nations Development Program website (http://hdr.undp.org/en/composite/HDI), whereas Poisson regression analysis was used to explore the association of one standard deviation of HDI with total IM and its components. All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Ethical approval: Not required.

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, total IMR per 1000 livebirths in infants born to Greek and non-Greek mothers, as well as HDI values, in Greece, during the study period, are shown in Table 1. Moreover, infant deaths and total infant mortality rates (IMR) by place of residence (Urban/Semi-urban *vs.* Rural) are shown in Suppl. 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).

Overall, during the study-period, among infants born to 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, p=0.02 for each), albeit differentially by place of residence (Table 2); significant decline of IMR trends (-3.5%; -4.6% to -2.4% annually, p<0.0001) and all its components was observed among infants born to Greek mothers living in urban areas whereas, among infants born to Greek mothers in rural areas, a significant increase of IMR trend was observed (+5.2%; 1.3% to 9.3% annually, p=0.01) resulting mainly from increased ENMR (+24.1%; 14.2% to 34.8% annually, p<0.0001). By contrast, among infants of non-Greek mothers, the low starting IMR increased significantly (+9.4%; 6.9% to 11.9% annually, p<0.0001), due to significant increases of ENMR, LNMR and PNMR (max ENMR: +12.5%; 8.6% to 16.5% annually, p<0.0001) leading to a non-significant pattern of IMR evolution for Greece overall (p=0.50) (Table 2). Further analysis by nationality of non-Greek mothers showed significant increases of IMR trends in all ethnic groups with average annual percent change 7.6% (95% CI; 4.2% to 11.1%) in infants born to Albanian mothers, 8.6% (3.7% to 13.8%) in infants born to mothers from Balkan countries and countries of the former Soviet Union, 9.4% (2.8% to 16.3%) in infants born to mothers from Asia, 9.4% (1.1% to 18.3%) in infants born to mothers from countries of the European Union or other developed countries, and 21.1% (11.0% to 32.3%) in infants born to mothers from Africa. HDI trends increased significantly, by 0.1% (95% CI 0.06% to 0.13%) annually during the study period. Inverse associations of HDI with IMR, ENMR and PNMR, restricted to Greek mothers' infants, were observed (Table 2).

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

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 associations of HDI with ENMR and IMR, but also PNMR, among infants born to Greek mothers.

Strengths of the present investigation, as contrasted to previously Greek-based published studies,[9,18,20,21,23] include the longest follow-up period of national data, namely since 2004, before the crisis, when the first data on maternal ethnicity became electronically available, to the latest available year 2016. Of great importance is also the fact that, for the first time, the maternal ethnicity was considered in the analyses explaining part, if not most, of the heterogeneity of trends through the study period. To this end, three complimentary statistical methodologies were used to describe the overall evolution depicted in Figure 1. Thus, we were able to enhance the validity of the results pertaining to the study of the evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which individual data have been available on a nationwide level among both deaths and livebirths during the study period. Calculation of IMR and its components was based on the number of livebirths; yet, the absence of a linkage system between birth and death data, as well as other official registries in Greece, has not allowed use of known determinants of socioeconomic deprivation or social coherence, such as parental education, employment/occupation, marital status, family income and household size. Neither were data on the role of biological factors, such as parental age, gestational age and birthweight, or multiplicity of pregnancy available for both the livebirths and deaths series.[5,19,24] Besides, the study period, with available information on maternal nationality and place of residence, was rather short leading to ITS analyses with few data points; however, ITS analysis can be used even for few observations; no log-transformation is needed but the results should be interpreted with caution as the power depends on various factors.[25] Lastly, analyses by specific cause of infant death were not set among the outcome measures of this study.

Assessing migration as a determinant of perinatal health outcome and infant death in the developed countries is a complex undertaking resulting in conflicting results of published studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor for unfavorable perinatal outcomes and increased neonatal and infant mortality,[18,26-33] especially if it coincides with a financial crisis, as was the case in Greece. Factors possibly contributing to the increased risk for poorer outcomes among children born to migrants include socioeconomic disadvantage, poor communication, discrimination, reduced utilization of health facilities, low quality of care, but also stress and consanguinity or differing attitudes to screening and termination of pregnancy associated with preterm birth, low birth weight or congenital anomalies and lethal inherited diseases.[26,30,34-36] By contrast, other studies present similar or even better perinatal health outcomes among some migrant groups than among natives ("healthy migrant effect/paradox").[26-28,37,38] Refugees have been recognized as the most vulnerable group suffering increased severe neonatal morbidity and infant mortality risk,[26,28] although no absolutely clear pattern regarding refugee or non-refugee status among migrants has been identified.[34]

In our study, starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers. Of note, the ratio of non-Greek infants among live births during 2009-2016 *vs.* 2004-2008 was only 1.32, whereas the respective figure among infant deaths was almost 3-fold (data not shown). Actually, in the pre-crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most of them of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece experienced an influx of refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.[16,17] It could be suggested that changes in the homogeneity of foreign mothers during the study period, in association with the country's economic difficulties, might have led from the "healthy migrant effect", observed before 2008, to the deterioration of IM indicators and IMR trends, afterwards, in infants born to non-Greek mothers. We did observe significant increases in IMR trends in all ethnic groups of non-Greek mothers during the study period, especially in infants born to mothers from Africa; however as the numbers by individual maternal nationality were rather small, this issue needs to be further studied.

Simultaneously with immigration to/through Greece, the country experienced the third wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left Greece since the onset of the economic crisis, in 2008, seeking new opportunities and employment in other countries, mainly Germany, the United Kingdom and the Netherlands.[39,40] The current emigration wave of Greeks involved mostly highly-educated people (the so called "brain-drain") of young age, leading to a decrease in the number of Greek women of childbearing age.[41] This fact, along with the decrease in the fertility rate by almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual number of livebirths in Greece by almost 23% during the period of the economic crisis.[41,42] Furthermore, the flow of mostly affluent and well educated people going outside Greece could also contribute to increases in IMR among Greek children following the crisis.

Indeed, the strongly decreasing IMR, especially ENMR, trends among Greek infants were stagnated after a lag time of ~four years of crisis and equalized with the previously sharply increasing trends among non-Greek maternal nationality infants; this time lag is reasonable[43] and in line with previous findings showing that following reductions in the government healthcare spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4 and 5 years later, respectively.[6] The irony is that the period 2012-2016, during which the crisis was deepening[13,14] and stricter economic austerity measures were applied,[44] disparities gap in IMR trends diminished against the Greek population; IMR trends deteriorated only in infants born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends approached an anelastic highest value up to 2011 with no fluctuation thereafter. The importance of two sub-analyses of IMR trends by maternal nationality (Greek vs. non-Greek) should be emphasized; when trends in the entire study population were assessed, year 2008, considered the year of crisis initiation, was misleadingly identified as a break in IMR and ENMR trends by joinpoint regression analysis, in line with findings of previous relevant studies in Greece which did not take into consideration the maternal nationality.[20]

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

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

The exact mechanisms leading to the disparities in trends of neonatal and infant mortality observed in this study remain to be further explored. Specific maternal, family and infant features, including detailed and punctual information on the causes of infant deaths, would have shed more light on the links between IMR trends and socioeconomic factors but were beyond the scope of this article and left for future research. Meanwhile, policies and programs should be implemented to mitigate the negative impact of the crisis on population and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of low income, or rural place of residence, should be specifically addressed and their rights to health protected. Barriers in the access of refugees to the Greek health care system have been identified; they are mostly related to language, culture, and inadequate information about the healthcare system, but also include difficulties in the coordination of Health Services, transportation problems, issues in obtaining expertise medical assessment in the camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for health and social care services, and administrative barriers, among others.[52] In response, the Greek government and several Non-Governmental Organizations initiated commendable actions, i.e. National Health System services free of charge for uninsured and vulnerable social groups including asylum seekers , translation services in public hospitals, access to specialist care/treatment with Gynecologists (mostly women), midwives, dentists, psychologists, and psychiatrists being lately included in the camp clinics;[52] these actions may have prevented deterioration of IMR which are being kept at steady levels after 2011 in infants of non-Greek mothers; efforts should be continued and intensified, however, as to ensure equity with local populations. Strong governmental integration policy for minorities paired with initiatives to improve social coherence, a deeply rooted mechanism for protection of health among those in need in the Greek society, along with further improvements in primary health care delivery could help to alleviate the cost in infant lives and ensure healthy adulthood.[32,51] Irrespective of the crisis, improvements in the quality of perinatal and neonatal care, including centralization of very preterm deliveries, establishment of regional perinatal centers, monitoring of the implementation of evidence-based practices in maternity and neonatal units, as well as increase in health expenditures, health care workforce, number of doctors and midwifes/nurses, could decrease ENMR, eventually leading to overall decrease in IMR in Greece.[50]

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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.

	Infants born to Greek mothers			Infants born to non-Greek mothers			HDI
Year	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.

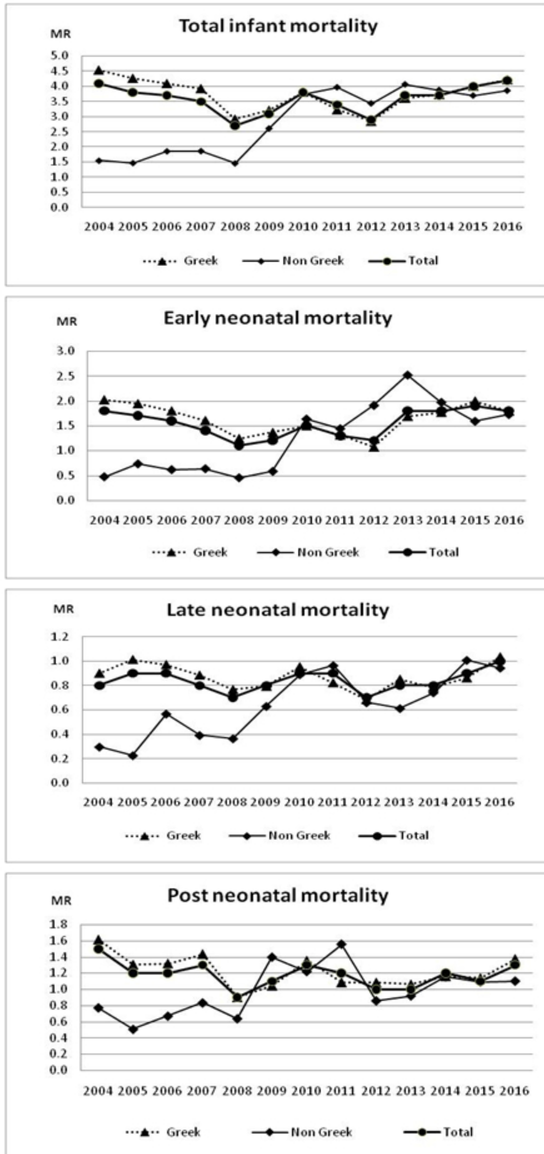
Variable	IMR			ENMR			LNMR			PNMR		
	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value	N	APC (95% CI)	p-value
Maternal nationality												
Greek	4238	**-0.9 (-1.7,-0.1)**	**0.02**	1849	-0.6 (-1.8,0.7)	0.35	995	-0.6 (-2.3,1.1)	0.46	1393	**-1.6 (-3.0,-0.2)**	**0.02**
Non-Greek	615	**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

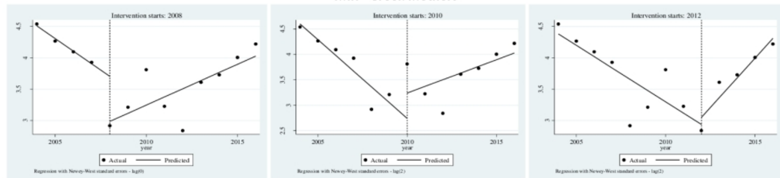


Evolution of Infant Early, Late and Post Neonatal Mortality Rates in Greece (2004-2016) overall and by maternal nationality

60x81mm (300 x 300 DPI)

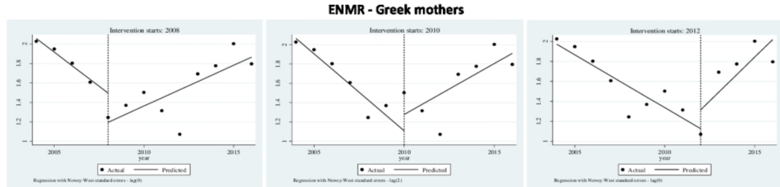
2008	2010	2012

IMR - Greek mothers



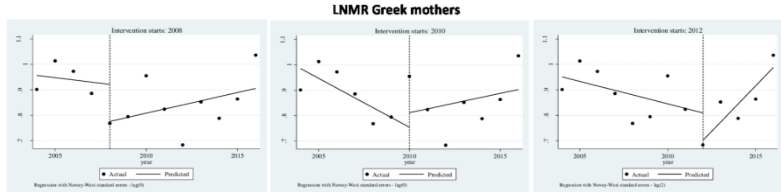
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.20	-0.23	-0.16	0.0001	-0.31	-0.38	-0.24	0.0001	-0.18	-0.28	-0.08	0.003
change of slope	-0.72	-1.17	-0.26	0.006	0.50	-0.29	1.59	0.19	0.11	-0.69	0.91	0.76
>year of interest	0.13	0.06	0.20	0.002	0.13	-0.03	0.29	0.10	0.31	0.21	0.41	0.0001

ENMR - Greek mothers



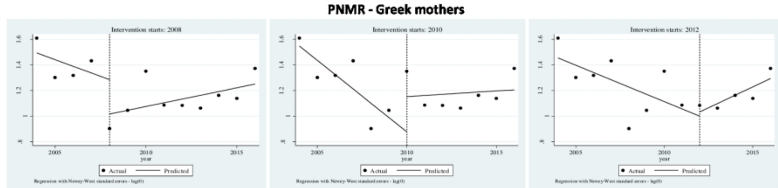
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.14	-0.18	-0.10	0.0001	-0.16	-0.20	-0.12	0.0001	-0.11	-0.15	-0.07	0.0001
change of slope	-0.30	-0.53	-0.07	0.02	0.17	-0.16	0.49	0.27	0.19	-0.35	0.73	0.45
>year of interest	0.08	0.04	0.12	0.001	0.11	0.03	0.18	0.01	0.18	-0.01	0.37	0.07

LNMR Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.01	-0.07	0.05	0.75	-0.04	-0.08	0.00	0.05	-0.02	-0.04	0.01	0.07
change of slope	-0.15	-0.34	0.05	0.12	0.06	-0.19	0.31	0.61	-0.11	-0.24	0.03	0.10
>year of interest	0.02	-0.01	0.04	0.23	0.02	-0.04	0.07	0.58	0.07	0.04	0.10	0.0004

PNMR - Greek mothers



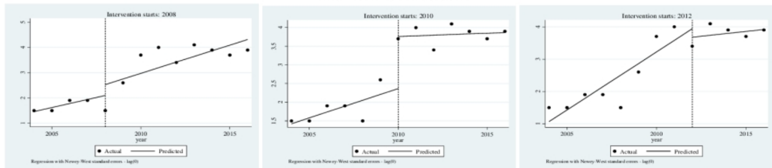
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.05	-0.18	0.08	0.39	-0.11	-0.18	-0.04	0.004	-0.06	-0.11	0.00	0.05
change of slope	-0.27	-0.66	0.12	0.15	0.28	-0.15	0.71	0.18	0.03	-0.32	0.38	0.84
>year of interest	0.03	-0.01	0.07	0.14	0.01	-0.07	0.09	0.81	0.07	0.0	0.12	0.03

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)

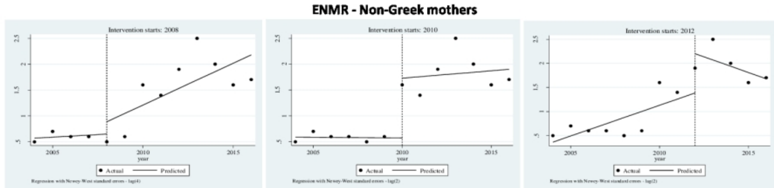
2008	2010	2012

IMR - Non-Greek mothers



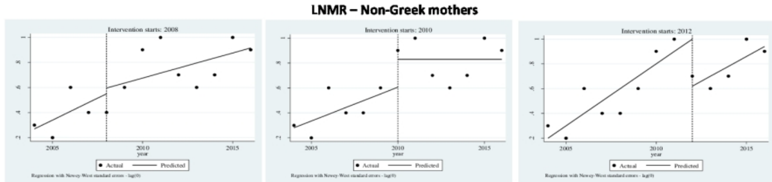
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.16	0.09	0.23	0.0001	0.16	-0.05	0.36	0.11	0.36	0.2	0.52	0.001
change of slope	0.43	-0.83	1.69	0.46	1.39	0.33	2.46	0.02	-0.26	-1.41	0.88	0.62
>year of interest	0.22	0.0	0.45	0.05	0.02	-0.05	0.08	0.57	0.06	-0.13	0.25	0.48

ENMR - Non-Greek mothers



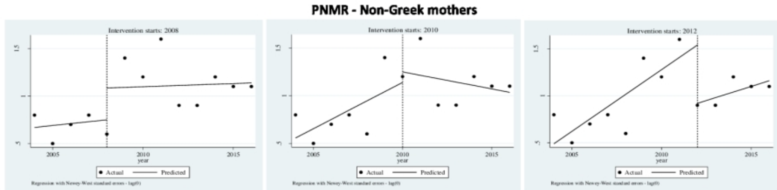
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.02	-0.02	0.06	0.32	-0.003	-0.03	0.03	0.83	0.13	0.03	0.23	0.02
change of slope	0.24	-0.41	0.89	0.43	1.16	0.63	1.68	0.001	0.81	-0.05	1.68	0.06
>year of interest	0.16	0.01	0.31	0.04	0.03	-0.10	0.16	0.63	-0.13	-0.28	0.02	0.08

LNMR – Non-Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.07	-0.02	0.16	0.13	0.05	0.01	0.10	0.03	0.10	0.05	0.15	0.001
change of slope	0.05	-0.40	0.49	0.82	0.22	-0.06	0.51	0.11	-0.38	-0.67	-0.09	0.02
>year of interest	0.04	-0.01	0.09	0.1	0.0	-0.06	0.06	0.99	0.08	0.01	0.15	0.03

PNMR - Non-Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.02	-0.11	0.15	0.74	0.10	-0.09	0.29	0.28	0.13	0.04	0.22	0.01
change of slope	0.33	-0.34	1.01	0.29	0.11	-0.81	1.03	0.79	-0.62	-1.09	-1.52	0.02
>year of interest	0.01	-0.09	0.11	0.89	-0.04	-0.12	0.05	0.36	0.06	0.02	0.10	0.01

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).

	Infants born to mothers living in urban/semiurban areas		Infants born to mothers living in rural areas	
Year	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

Research checklist- STROBE Statement—checklist

	Item No	Page number
Title and abstract	1	1
		3
Introduction		
Background/rationale	2	6-7
Objectives	3	7
Methods		
Study design	4	7-9
Setting	5	7
Participants	6	7-8
Variables	7	7-9
Data sources/ measurement	8*	*7-9*
Bias	9	N/A
Study size	10	N/A
Quantitative variables	11	7-9
Statistical methods	12	8-9
Results		
Participants	13*	9-10
Descriptive data	14*	9-10
Outcome data	15*	9-12
Main results	16	9-12
Other analyses	17	N/A
Discussion		
Key results	18	12
Limitations	19	12-13
Interpretation	20	14-18
Generalisability	21	17-18
Other information		
Funding	22	25

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

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Keywords:	Neonates, Mortality rates, Infant deaths, perinatal care, financial crisis

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

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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.

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

CONCLUSIONS

HDI and rural residence were significantly associated with IMR. The strongly decreasing IMR trends among Greek-mothers' infants were stagnated after a lag time of ~four years of crisis approximating the previously sharply increasing trends among non-Greeks.

Strengths of this study

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

Limitations

- Absence of a linkage system between birth and death data.
- 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 disproportionally 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

proportion of individuals at risk of poverty or social exclusion climbed to almost 36% in 2016. Total health expenditures and government expenditure on health care were both decreased by 34% per capita over the period 2008-2016,[13,14] whereas unmet healthcare needs increased.[15] Besides, during the last years, Greece experienced large refugee flows[16,17] with an anticipated negative impact on the country's economy and population health indicators. Adverse effects of financial crisis on perinatal factors, such as low birth weight, preterm birth and stillbirth rates, have been also observed;[18,19] however, sparse data exist regarding the potential association of the crisis with IMR. It has been initially reported that during the period 2003-2012, IMR in Greece did not differ between the pre-crisis and crisis period whereas, a later study showed that IMR increased between 2010 and 2015 as contrasted to the steady decrease observed during the preceding decade.[20,21] Ecological correlations may prone, however, to fallacies, whereas the different parts shaping the two main components of IM, namely neonatal (NM) and post neonatal mortality (PNM), should have been distinctly examined along with other factors possibly influencing the infants' health, especially socioeconomic status and access to health care delivery.

The aims of the current study were to explore time trends in early (<7 days of life) and late (7-27 days) neonatal, post neonatal (28-364 days) and total IM (0-364 days) in Greece during the period 2004-2016 after taking into account nationality and place of residence, as well as changes in the Human Development Index (HDI) during the study period as a proxy of individual and collective measures of socioeconomic impact and health care access.

Materials and Methods

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

one, infant deaths; linkage of the two files was not possible as the personal identification number was not available in ELSTAT. Information on maternal demographic characteristics, such as nationality and place of residence, as well as on the infants' age at death, was also provided.

Mortality rates were calculated for infant (IM), early neonatal (0-6 days) (ENM), late neonatal (7-27 days) (LNM) and post neonatal (28-364 days) period (PNM) using respective numbers of deaths over the number of livebirths per year. Annual percent of change (APC) during the study period was initially estimated through univariate Poisson regression analysis using the underlying population of each set as an offset variable. Subsequently, data were stratified and analyzed by maternal nationality (Greek *vs.* non-Greek) and place of residence (Urban/Semi-urban *vs.* Rural). Joinpoint regression analysis[22] was thereafter applied to automatically derive, by a software program, different segments in the mortality evolution curves overall, as well as those by maternal nationality and place of residence. In details, the Joinpoint regression analysis is applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. The location of the joinpoint is not known a priori and is to be estimated from the data. Therefore, the software takes trend data (e.g. IM rates) and fits the simplest joinpoint model based on the data. The user supplies the minimum and maximum number of joinpoints. The algorithm starts with the minimum number of joinpoint (e.g. 0 joinpoints, which is a straight line) and tests whether more joinpoints are statistically significant and must be added to the model (up to that maximum number). Significance is tested using a Monte Carlo Permutation method. In all models examined in this study, a minimum number of 0 joinpoints and a maximum one of 2 joinpoints were tested. Interrupted Time Series (ITS) analyses were also undertaken as a sensitivity analysis to further explore the effect of crisis on IMR and its components in alternative prespecified years, notably 2008, considered to indicate the initiation of the crisis in Greece -as the value of the Gross Domestic Product of the country was maximum at that year but dropped afterwards (Source: Aggregate National Accounts)-, and in two successive periods two years apart (2010 and 2012), to control for possible time lags in observing the impact of the crisis. All ITS models were verified and appropriately adjusted for possible auto-correlation; autoregressive integrated moving - average models were used to control for autocorrelation and to estimate treatment effects over multiple periods. In our ITS analysis a slope "<year of interest" is fitted until the introduction of the crisis, ">year of interest" represents the change in the level of the mortality immediately following the initiation of the crisis and "change of slope" represents the differences between pre and post crisis intervention slopes.

Human development index (HDI) is a summary measure of average achievements of a country's population in three areas including life expectancy, education and *per capita* income indicators. Annual HDI values for the underlying populations in the year of death were extracted from the United Nations Development Program website (http://hdr.undp.org/en/composite/HDI), whereas Poisson regression analysis was used to explore the association of one standard deviation of HDI with total IM and its components. All statistical analyses were performed using the SAS software (V9.4, SAS Institute Inc.), Stata software program, version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP) and Joinpoint Regression Program (Joinpoint Regression Program, Version 4.5.0.1 - June 2017; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute).

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Ethical approval: Not required.

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, total IMR per 1000 livebirths in infants born to Greek and non-Greek mothers, as well as HDI values, in Greece, during the study period, are shown in Table 1. Moreover, infant deaths and total infant mortality rates (IMR) by place of residence (Urban/Semi-urban *vs.* Rural) are shown in Suppl. 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).

Overall, during the study-period, among infants born to Greek mothers, Poisson regression analyses showed decreasing trends in IMR and PNMR (-0.9%; 95% CI -1.7% to -0.1% and -1.6%; -3.0% to -0.2% annually, respectively, p=0.02 for each), whereas no significant change in ENMR and LNMR was observed (Table 2). Interestingly, mortality trends changed differentially by place of residence; significant decline of IMR trends (-2.1%; -2.9% to -1.3% annually, p<0.0001) and all its components was observed among infants born to Greek mothers living in urban areas whereas, among infants born to Greek mothers in rural areas, a significant increase of IMR (+10.6%; 7.6% to 13.6% annually, p=0.002), ENMR (+24.1%; 17.0% to 31.5% annually, p<0.0001) and LNMR trend (+12.7%; 6.5% to 19.2% annually, p<0.0001) was observed (Table 2). By contrast, among infants of non-Greek mothers, the low starting IMR increased significantly (+9.4%; 6.9% to 11.9% annually, p<0.0001), due to significant increases of ENMR, LNMR and PNMR (max ENMR: +12.5%; 8.6% to 16.5% annually, p<0.0001) leading to a non-significant pattern of IMR evolution for Greece overall (p=0.50) (Table 2). Further analysis by nationality of non-Greek mothers showed significant increases of IMR trends in all ethnic groups with average annual percent change 7.6% (95% CI; 4.2% to 11.1%)in infants born to Albanian mothers, 8.6% (3.7% to 13.8%) in infants born to mothers from Balkan countries and countries of the former Soviet Union, 9.4% (2.8% to 16.3%) in infants born to mothers from Asia, 9.4% (1.1% to 18.3%) in infants born to mothers from countries of the European Union or other developed countries, and 21.1%

(11.0% to 32.3%) in infants born to mothers from Africa. HDI trends increased significantly, by 0.1% (95% CI 0.06% to 0.13%) annually, during the study period. Inverse associations of HDI with IMR, ENMR and PNMR, restricted to Greek mothers' infants, were observed (Table 2).

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

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

The results of ITS analyses in the preset years 2008, 2010 and 2012 are shown in Figures 2 and 3. Compared to the joinpoint regression showing non-significant increases in IMR from 2012 to 2016 for infants born to Greek mothers, ITS analysis showed a significant increase in IMR (p=0.0001) in this population during the same time period and further identified significant increases in LNMR (p=0.0004) and PNMR trends (p=0.03). As regards the non-significant increases of ENMR trends after the year 2011 by joinpoint regression in infants born to Greek mothers (p=0.06), ITS analysis showed a non-significant increase during the post 2012 time period (p=0.07); however, a significant increase during the post 2010 time period in these infants was observed (p=0.01) (Figure 2). In infants born to non-Greek mothers, while a significant increase in IMR trends was found by joinpoint regression analyses during the period 2004-2011, by ITS analyses -depending on when the year of interest was being defined (2010 or 2012)- the increase was either not significant (2004-2010, p=0.11) or significant (2004-2012, p=0.001); no change in IMR was identified by ITS analysis over the 2010-2016 or 2012-2016 time periods in non-Greek mothers' infants (Figure 3).

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 mothers' infants, differentials by place of residence and also increases in IM indices among Greek mothers' infants noted ~four years after the crisis initiation. Specifically, the "brake" of 2012 identified, by joint point regression analysis, non-significant increases of~10% annually, in IMR and ENMR trends, whereas by ITS analyses, significant increases in IMR, LNMR and PNMR trends were observed thereafter among infants born to Greek mothers, a fact indicating how sensitive the results are depending on the statistical method used. Changes in HDI during the study period were also reflected in the inverse associations of HDI with ENMR and IMR, but also PNMR, among infants born to Greek mothers.

Strengths of the present investigation, as contrasted to previously Greek-based published studies,[9,18,20,21,23] include the longest follow-up period of national data, namely since 2004, before the crisis, when the first data on maternal ethnicity became electronically available, to the latest available year 2016. Of great importance is also the fact that, for the first time, the maternal ethnicity was considered in the analyses explaining part, if not most, of the heterogeneity of trends through the study period. To this end, three complimentary statistical methodologies were used to describe the overall evolution depicted in Figure 1. Thus, we were able to enhance the validity of the results pertaining to the study of the evolution of individual IMR components, namely ENMR, LNMR and PNMR, in association with socioeconomic factors (i.e maternal nationality, place of residence and HDI) for which individual data have been available on a nationwide level among both deaths and livebirths during the study period. Calculation of IMR and its components was based on the number of livebirths; yet, the absence of a linkage system between birth and death data consists a limitation of the study. The absence of a linkage system, as well as that of other official registries in Greece, has not allowed use of known determinants of socioeconomic deprivation or social coherence, such as parental education, employment/occupation, marital status, family income and household size. Neither were data on the role of biological factors, such as parental age, gestational age and birthweight, or multiplicity of pregnancy available for both the livebirths and deaths series.[5,19,24] Besides, the study period, with available information on maternal nationality and place of residence, was rather short leading to ITS analyses with few data points; however, ITS analysis can be used even for few observations; no log-transformation is needed but the results should be interpreted with caution as the power depends on various factors.[25] Lastly, analyses by specific cause of infant death were not set among the outcome measures of this study.

Assessing migration as a determinant of perinatal health outcome and infant death in the developed countries is a complex undertaking resulting in conflicting results of published studies. Specifically, some studies, have shown that ethnic minority is a significant risk factor for unfavorable perinatal outcomes and increased neonatal and infant mortality,[18,26-33] especially if it coincides with a financial crisis, as was the case in Greece. Factors possibly contributing to the increased risk for poorer outcomes among children born to migrants include socioeconomic disadvantage, poor communication, discrimination, reduced utilization of health facilities, low quality of care, but also stress and consanguinity or differing attitudes to screening and termination of pregnancy associated with preterm birth, low birth weight or congenital anomalies and lethal inherited diseases.[26,30,34-36] By contrast, other studies present similar or even better perinatal health outcomes among some migrant groups than among natives ("healthy migrant effect/paradox").[26-28,37,38] Refugees have been recognized as the most vulnerable group suffering increased severe neonatal morbidity and infant mortality risk,[26,28]although no absolutely clear pattern regarding refugee or non-refugee status among migrants has been identified.[34]

In our study, starting rates of IMR and its components among infants born to non-Greek mothers were lower compared to those of Greek mothers. Of note, the ratio of non-Greek infants among live births during 2009-2016 *vs.* 2004-2008 was only 1.32, whereas the respective figure among infant deaths was almost 3-fold (data not shown). Actually, in the pre-crisis era, non-Greek mothers of newborns comprised mainly economic migrants, most of them of Albanian nationality living for many years, or even born, in Greece. After 2008, Greece experienced an influx of refugees with the majority of them fleeing from war and terror in Syria, Occupied Palestinian Territory, but also from Afghanistan, Iraq and other countries.[16,17] It could be suggested that changes in the homogeneity of foreign mothers during the study period, in association with the country's economic difficulties, might have led from the "healthy migrant effect", observed before 2008, to the deterioration of IM indicators and IMR trends, afterwards, in infants born to non-Greek mothers. We did observe significant increases in IMR trends in all ethnic groups of non-Greek mothers during the study period, especially in infants born to mothers from Africa; however as the numbers by individual maternal nationality were rather small, this issue needs to be further studied.

Simultaneously with immigration to/through Greece, the country experienced the third wave of mass emigration in the 20th and 21st centuries; over 400,000 Greek citizens left Greece since the onset of the economic crisis, in 2008, seeking new opportunities and employment in other countries, mainly Germany, the United Kingdom and the Netherlands.[39,40] The current emigration wave of Greeks involved mostly highly-educated people (the so called "brain-drain") of young age, leading to a decrease in the number of Greek women of childbearing age.[41] This fact, along with the decrease in the fertility rate by almost 10% between 2008 and 2016, contributes significantly to the reduction in the annual number of livebirths in Greece by almost 23% during the period of the economic crisis.[41,42] Furthermore, the flow of mostly affluent and well educated people going outside Greece could also contribute to increases in IMR among Greek children following the crisis.

Indeed, the strongly decreasing IMR trends among Greek infants were stagnated after a lag time of ~four years of crisis and equalized with the previously sharply increasing trends among non-Greek maternal nationality infants; this time lag is reasonable[43] and in line with previous findings showing that following reductions in the government healthcare spending in Europe, the greatest negative effect on neonatal and post neonatal mortality was 4 and 5 years later, respectively.[6] The irony is that the period 2012-2016, during which the crisis was deepening[13,14] and stricter economic austerity measures were applied,[44] disparities gap in IMR trends diminished against the Greek population; IMR trends deteriorated only in infants born to Greek mothers, whereas in infants born to non-Greek mothers IMR trends approached an anelastic highest value up to 2011 with no statistically significant change thereafter.

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

Among the three IMR components, ENMR seemed to be the most "sensitive" in reflecting adverse impacts on child health. Specifically, ENMR was overall positively associated with rural place of residence of Greek mothers' children and also presented the most sizeable increase among IM indices in non-Greeks (Table 2). Moreover, among the three IM components, ENMR was the first or the only one, -depending on the statistical method used-, that increased after the crisis initiation in infants born to Greek mothers. ENMR, in developed countries, including Greece, represents more than 70% of neonatal deaths on account mainly of prematurity/low birth weight and congenital anomalies.[14,48-51] Actually, it reflects perinatal health and care during pregnancy and labor, and also postnatal care in the first week of life.[50] Increased incidence of impaired perinatal parameters including low birth weight, prematurity, and increased maternal age and rate of caesarian section, have been reported during the years of the economic decline in Greece.[18,19] Cuts in public health expenditures between 2008 and 2016, reduction in health care workforce and pediatric nurses, as well as reduction in the number of obstetrics beds, obstetricians and midwifes (-45.5%, -60.2% and -27.5%, respectively)[14] could possibly explain, at least in part, the observed positive ENMR trends during the post-crisis period in Greece.

The exact mechanisms leading to the disparities in trends of neonatal and infant mortality observed in this study remain to be further explored. Specific maternal, family and infant features, including detailed and punctual information on the causes of infant deaths, would have shed more light on the links between IMR trends and socioeconomic factors but were beyond the scope of this article and left for future research. Meanwhile, policies and programs should be implemented to mitigate the negative impact of the crisis on population and infant health in Greece. Vulnerable groups, such as mothers of non-Greek nationality, of low income, or rural place of residence, should be specifically addressed and their rights to health protected. Barriers in the access of refugees to the Greek health care system have been identified; they are mostly related to language, culture, and inadequate information about the healthcare system, but also include difficulties in the coordination of Health Services, transportation problems, issues in obtaining expertise medical assessment in the camps, lack of continuity of care, financial difficulties in making out-of-pocket payments for health and social care services, and administrative barriers, among others.[52] In response, the Greek government and several Non-Governmental Organizations initiated commendable actions, i.e. National Health System services free of charge for uninsured and vulnerable social groups including asylum seekers, translation services in public hospitals, access to specialist care/treatment with Gynecologists (mostly women), midwives, dentists, psychologists, and psychiatrists being lately included in the camp clinics;[52] these actions may have prevented deterioration of IMR which are being kept at steady levels after 2011-2012 in infants of non-Greek mothers; efforts should be continued and intensified, however, as to ensure equity with local populations. Strong governmental integration policy for minorities paired with initiatives to improve social coherence, a deeply rooted mechanism for protection of health among those in need in the Greek society, along with further improvements in primary health care delivery could help to alleviate the cost in infant lives and ensure healthy adulthood.[32,51] Irrespective of the crisis, improvements in the quality of perinatal and neonatal care, including centralization of very preterm deliveries, establishment of regional perinatal centers, monitoring of the implementation of evidence-based practices in maternity and neonatal units, as well as increase in health expenditures, health care workforce, number of doctors and midwifes/nurses, could decrease ENMR, eventually leading to overall decrease in IMR in Greece.[50]

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Data sharing: Data are available upon request from ELSTAT (http://www.statistics.gr/el/statistical-data-request)

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Competing interests statement

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

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.

	Infants born to Greek mothers			Infants born to non-Greek mothers			HDI
Year	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

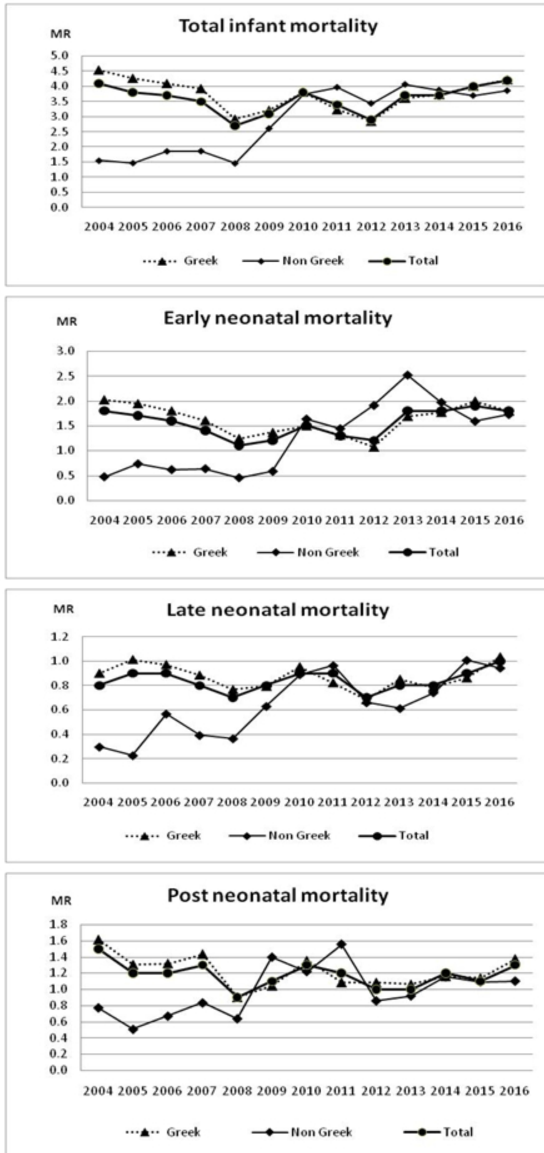
Table 3. Joinpoint regression derived Annual Percent of Change (APC) and 95% Confidence Intervals (CI) of infant (IMR), early neonatal (ENMR), late neonatal (LNMR) and post neonatal (PNMR) mortality rates by maternal nationality.

	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.



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

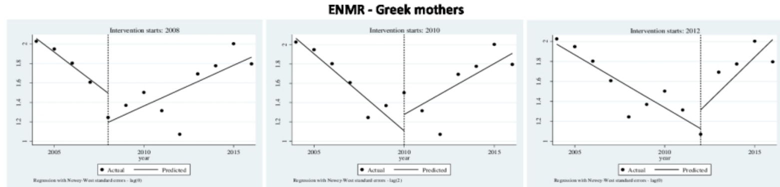
60x81mm (300 x 300 DPI)

2008	2010	2012

IMR - Greek mothers

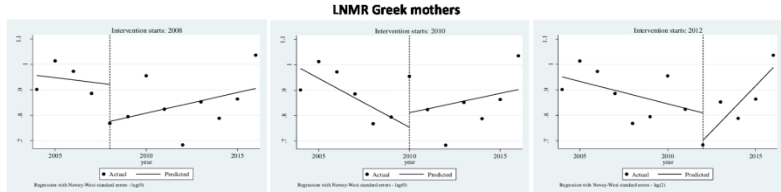
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.20	-0.23	-0.16	0.0001	-0.31	-0.38	-0.24	0.0001	-0.18	-0.28	-0.08	0.003
change of slope	-0.72	-1.17	-0.26	0.006	0.50	-0.29	1.59	0.19	0.11	-0.69	0.91	0.76
>year of interest	0.13	0.06	0.20	0.002	0.13	-0.03	0.29	0.10	0.31	0.21	0.41	0.0001

ENMR - Greek mothers



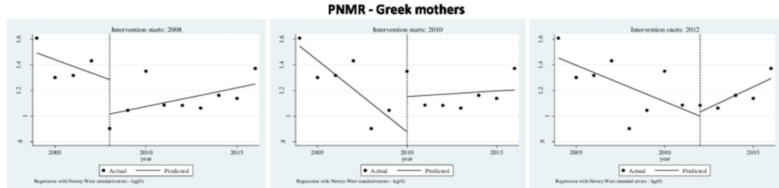
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.14	-0.18	-0.10	0.0001	-0.16	-0.20	-0.12	0.0001	-0.11	-0.15	-0.07	0.0001
change of slope	-0.30	-0.53	-0.07	0.02	0.17	-0.16	0.49	0.27	0.19	-0.35	0.73	0.45
>year of interest	0.08	0.04	0.12	0.001	0.11	0.03	0.18	0.01	0.18	-0.01	0.37	0.07

LNMR Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.01	-0.07	0.05	0.75	-0.04	-0.08	0.00	0.05	-0.02	-0.04	0.01	0.07
change of slope	-0.15	-0.34	0.05	0.12	0.06	-0.19	0.31	0.61	-0.11	-0.24	0.03	0.10
>year of interest	0.02	-0.01	0.04	0.23	0.02	-0.04	0.07	0.58	0.07	0.04	0.10	0.0004

PNMR - Greek mothers



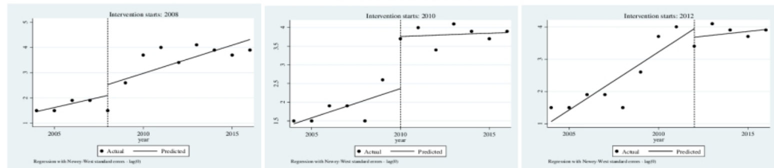
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	-0.05	-0.18	0.08	0.39	-0.11	-0.18	-0.04	0.004	-0.06	-0.11	0.00	0.05
change of slope	-0.27	-0.66	0.12	0.15	0.28	-0.15	0.71	0.18	0.03	-0.32	0.38	0.84
>year of interest	0.03	-0.01	0.07	0.14	0.01	-0.07	0.09	0.81	0.07	0.0	0.12	0.03

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)

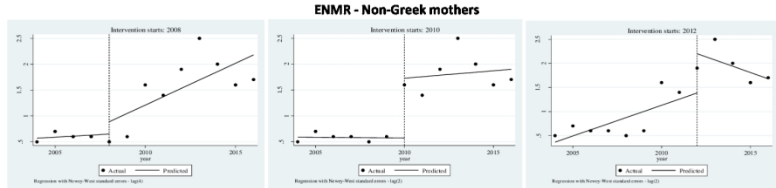
2008	2010	2012

IMR - Non-Greek mothers



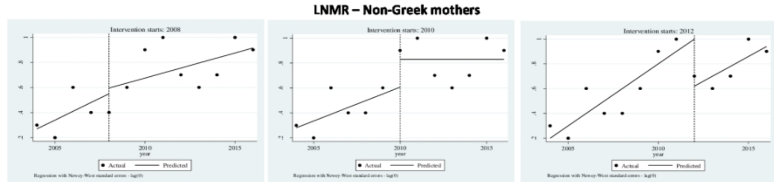
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.16	0.09	0.23	0.0001	0.16	-0.05	0.36	0.11	0.36	0.2	0.52	0.001
change of slope	0.43	-0.83	1.69	0.46	1.39	0.33	2.46	0.02	-0.26	-1.41	0.88	0.62
>year of interest	0.22	0.0	0.45	0.05	0.02	-0.05	0.08	0.57	0.06	-0.13	0.25	0.48

ENMR - Non-Greek mothers



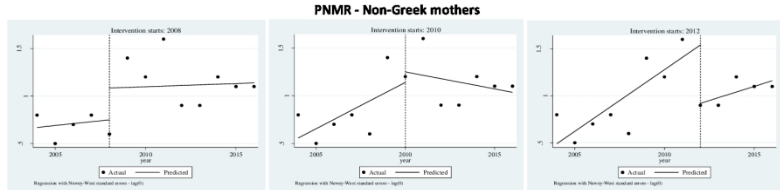
Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.02	-0.02	0.06	0.32	-0.003	-0.03	0.03	0.83	0.13	0.03	0.23	0.02
change of slope	0.24	-0.41	0.89	0.43	1.16	0.63	1.68	0.001	0.81	-0.05	1.68	0.06
>year of interest	0.16	0.01	0.31	0.04	0.03	-0.10	0.16	0.63	-0.13	-0.28	0.02	0.08

LNMR – Non-Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.07	-0.02	0.16	0.13	0.05	0.01	0.10	0.03	0.10	0.05	0.15	0.001
change of slope	0.05	-0.40	0.49	0.82	0.22	-0.06	0.51	0.11	-0.38	-0.67	-0.09	0.02
>year of interest	0.04	-0.01	0.09	0.1	0.0	-0.06	0.06	0.99	0.08	0.01	0.15	0.03

PNMR - Non-Greek mothers



Period	Coef.	95% CI		p-value	Coef.	95% CI		p-value	Coef.	95% CI		p-value
<year of interest	0.02	-0.11	0.15	0.74	0.10	-0.09	0.29	0.28	0.13	0.04	0.22	0.01
change of slope	0.33	-0.34	1.01	0.29	0.11	-0.81	1.03	0.79	-0.62	-1.09	-1.52	0.02
>year of interest	0.01	-0.09	0.11	0.89	-0.04	-0.12	0.05	0.36	0.06	0.02	0.10	0.01

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).

	Infants born to mothers living in urban/semiurban areas		Infants born to mothers living in rural areas	
Year	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

Research checklist- STROBE Statement—checklist

	Item No	Page number
Title and abstract	1	1
		3
Introduction		
Background/rationale	2	6-7
Objectives	3	7
Methods		
Study design	4	7-9
Setting	5	7
Participants	6	7-8
Variables	7	7-9
Data sources/ measurement	8*	*7-9*
Bias	9	N/A
Study size	10	N/A
Quantitative variables	11	7-9
Statistical methods	12	8-9
Results		
Participants	13*	9-10
Descriptive data	14*	9-10
Outcome data	15*	9-12
Main results	16	9-12
Other analyses	17	N/A
Discussion		
Key results	18	12
Limitations	19	12-13
Interpretation	20	14-18
Generalisability	21	17-18
Other information		
Funding	22	25