Author’s response to reviews

Title: Maternal age and Infant Mortality in two Sicilian districts: a retrospective follow up study.

Authors:

Walter Mazzucco (waltermazzucco@unipa.it)
Rosanna Cusimano (rosanna.cusimano@libero.it)
Maurizio Macaluso (macaluso@comcast.net)
Claudio La Scola (clasc@libero.it)
Giovanna Fiumanò (achille.cernigliaro@regione.sicilia.it)
Salvatore Scondotto (salvatore.scondotto@regione.sicilia.it)
Achille Cernigliaro (achille_c@libero.it)
Giovanni Corsello (giocors@alice.it)
Giuseppe La Torre (giuseppe.latorre@rm.unicatt.it)
Francesco Vitale (francesco.vitale@unipa.it)

Version: 2 Date: 4 May 2011

Author’s response to reviews:

To Consulting Editor and Reviewers
BMC Public Health

Dear Sirs,

My co-authors and I are grateful for the useful comments and we hope that the revised manuscript (enclosed) meets with your approval.

Below are point-by-point responses to the comments.

We hope that the manuscript, is now suitable for publication in “BMC Public Health”.

Best regards.
Walter Mazzucco

Reviewer's report
Title: Infant Mortality and maternal age in two Sicilian districts: a retrospective study.
Version: 1 Date: 22 December 2010
Reviewer: David A Paul
Reviewer's report:
The study of Mazzucco et al. Infant mortality and maternal age in two Sicilian districts: A retrospective study is a retrospective evaluation of infant and neonatal
mortality in two Sicilian districts. This investigation studies an important topic, the affect of maternal age on infant mortality. The authors conclude that infants born to older mothers (>40) in Messina district have greater odds of dying compared to infants born to older mothers in Palermo.

• The objectives are well defined, but broad in nature.
• Methods are appropriate.
• The data analyses are generally sound. However, I question whether IMR in women >40 in each district really differ. See comments below.
• Manuscript does adhere to standard for reporting.
• The authors do a nice job explaining the limitations of the study including missing data. Correcting for birth distribution of missing data is also helpful in supporting the results.
• Previous work is acknowledged.
• Title is appropriate. Abstract, is well written but needs some revision of the conclusion. See comments below.
• Writing is acceptable.

Major Compulsory Revisions:

1. The conclusions in the abstract should match more closely the conclusions in the Discussion—that the increase in IMR in Messina is due to an increase in mortality in infants born to older mothers, unrelated to an increase in births in this population.
   1. We have modified the abstract as suggested.
   (Abstract conclusions, last paragraph): “The association between advanced maternal age and infant deaths in the Messina district was due in part to the excess of newborns from advanced age mothers, but also to increased risk of death among such newborns. The significant interaction between district of residence and maternal age indicated that the IMR excess in the Messina district cannot be explained by disproportionately high live birth rates among older mothers, and suggested the hypothesis that health care facilities in the Messina district could be less well prepared to provide assistance to the excess of high risk pregnancies and deliveries, as compared to Palermo district.”

2. The authors define NMR as death in the 1st week of life. The standard definition for NMR is death is the 1st 28 days of life. Is NMR defined differently in Italy? Unless this is the case, the authors need to either rename the deaths in the 1st week as something other than NMR (early NMR) or recalculate the data
using the standard definition. Defining NMR as deaths in the 1st week is also problematic for the classification of post-neonatal MR as it pushes more infants into this category.

2. The reviewer’s observation is correct. Whereas we used the standard definition (death in the first 28 days of life) in computing the NMR and other parts of data analysis, we incorrectly defined neonatal death in the methods section. We have changed the text to reflect the correct definition (Statistical methods section, line 2) “For each district and year, IMRs were computed by dividing the number of infant deaths by the number of infants born alive, and multiplying the result by 1000. Similarly, NMR (death occurred in the first 28 days of life) and post-neonatal MR (after the first 28 days of life) were computed by restricting the numerator to the appropriate interval and dividing by the same denominator.”

3. More demographic information regarding the districts should be provided for the reader. How many NICUs are in each district? Are Reproductive Endocrinology/Infertility Services available in each district? High risk OB services? Are the rates of multiple births available from each district? It would be helpful to know the total number of births and premature births in each district.

3. We have provided additional information about NICUs, but we note that data reported from the Italian MAC registry have information on the district of the clinics where procedures were performed rather than on the district of residence of the women who used MAC. We have changed the text (Methods section, third paragraph) “The two districts differed by geographical and demographical characteristics as well for organization aspects: in the Palermo district 5 NICU are located in 5 different hospitals concentrated in the metropolitan area of Palermo, providing for a population of about 1,2 inhabitants and 13071 births per year (Central Institute of Statistics, year 2006); in the Messina district 5 NICU are located in 5 different hospitals, two large medical centres in the metropolitan area of Messina, and three small hospitals distributed in the district, providing for a population of 1,6 inhabitants and 5656 births per year (Central Institute of Statistics, year 2006). Furthermore, 16 MAC centres were active in the Palermo district, while two in the Messina district. It was not possible to assess use of MAC according to the district of residence of the patients. Thus, we cannot state whether MAC-related births were more common in Palermo or in Messina.”

4. Although the proportion of VLBW infants who died is similar in each district, the NMRs are very different. This highlights the point made above, readers need to know more about NICU availability. The authors state that twice as many infants were admitted to NICU in Messina. Why was this case with similar BW distribution? Some data on NICU admission is presented at the end of Table 2. Please clarify what is meant by “Presence” in this table.
4. We have modified along the text (and also table 2, by inserting a brief legend), according to previous data originally presented in table as follows: (Results section, Second Page, second paragraph): “A NICU was present at the hospital of delivery more often for infant deaths in the Messina district (89.7%) than in the Palermo district (78.6%), but the difference did not achieve statistical significance (p= 0.06). The deceased infants were admitted to a NICU slightly more often in the Messina district (97.1%) than in the Palermo district (90.1%), but the excess was not statistically significant (Fisher’s exact test, p= 0.13).”

5. Authors need to explain why there was an increase in deaths from prematurity in Messina without any difference in the distribution of birthweight or gestation. This would suggest either a difference in registration/classification of deaths or difference in quality of NICU care.

5. The reviewer should consider that we are reporting the distribution of deceased infants by birth weight and gestational age, not mortality rates by these categories. Because the numerator of the rate is both a function of the size of the denominator (unknown) and of the rate (also unknown), it is not possible to address the reviewer’s comment with the data at hand. Overall, the data indicate that the majority of infant deaths were preterm and low birth weight: the differences between districts should not distract from the common characteristics. We also note that the data on cause of death indicate an excess of prematurity in Messina and an excess of birth defects in Palermo, and that both categories of causes are associated with low birth weight. Thus, we perceive these findings as consistent.

6. Please provide data on multiple births in table 2. The authors speculate that the increase in IMR in older women is secondary to IVF, multiple births and low birth weight. The distribution in birthweight did not differ in the infants who died. The study would be strengthened if evidence were presented that the regions differed in birthweight, multiple births or infertility procedures. This information is really needed to strengthen the speculation of the authors.

6. Available sources do not provide reliable data on multiple births or infertility procedures by district of residence.

7. In Table 3, although the Odds ratios differ in magnitude for women >40, the 95% overlap for the 2 districts. Is there really a difference between regions given this overlap? It is also curious why there is no maternal age affect in the 35-39 category in either region? Please speculate.

7. The reviewer is correct that CIs overlap for comparison between specific categories, but we base our inference on a formal test of the interaction between age and district of residence. This test is more powerful and its result led to
rejecting the null hypothesis of a common effect of age in the two districts.

Discretionary Revisions:
1. Some of the abbreviations are not standard and difficult to follow including RenCaM, BC, ISTAT, ASP, SPO.
   1. Abbreviations have been replaced as follows:
      ReNCam with Death Causes Register
      ISTAT with Central Institute of Statistics
      ASP with District Health Agency
      SDO with Hospital Discharge Summaries
      BC with Birth delivery Centres

2. Please clarify how births were classified for women residing outside of the districts who delivered in the districts and for women residing in the districts who may have delivered elsewhere.

2. Within Death Causes registers every deceased subject has a district-code related to the mother’s residency, furthermore, every district Death Causes register is cross-linked together at regional level. In both cases we were confident to define and include deceased infants in the study, excluding subjects when inappropriately recorded in the Death Causes registries, and including deceased subjects born elsewhere to women residing in each of the two districts.

To better clarify inclusion criteria, the text was modified as follows: (Methods section, first and second paragraph) “In Italy infant death data is collected at the district level using standard forms designed by the Central Institute of Statistics and elaborated by its central office in Rome. In Sicily, each District Health Agency keeps a copy of the vital records and maintains an identifiable death registry (Death Causes Register), which allows local and regional (Regional Death Causes Register) use of the data and integration with other data sources, such as the Hospital Discharge Summaries.

We have identified in Death Causes Registers of Palermo and Messina districts all deaths during the first year of life recorded among infants born to residents in 2004-2006. Every deceased subject had a district-code related to mother’s residency that was used to appropriately record in the Death Causes Registers also deceased subjects born in a district different from the one where mothers were resident. Access to the hospital records pertaining to the admission closest to the time of death of each hospitalized included case was authorized by the district health agencies. Available hospital charts, as well as Death Causes Register and Hospital Discharge Summaries records, were abstracted using a standardized form designed to capture information on potential determinants of infant death.”

Level of interest: An article whose findings are important to those with closely related research interests
Reviewer’s report
Title: Infant Mortality and maternal age in two Sicilian districts: a retrospective study.
Version: 1 Date: 19 March 2011
Reviewer: Christy Okoromah
Reviewer’s report:
Reviews Comments on the article:
Re: 'Infant Mortality and maternal age in two Sicilian districts: a retrospective study.'

Compulsory Revisions
1. Is the question posed by the authors well defined?
   • The research question is not clear and it appears dissimilar in the abstract and
     the main manuscript
   1a. We have changed the abstract as follows: (Abstract background, second paragraph): “The present study compared a high IMR/NMR district (Messina) with a low IMR/NMR district (Palermo) during the period 2004-2006 to evaluate potential determinants of the IMRs’ differences between the two districts and specifically the impact of maternal age”
     • The authors should limit the aim of the study to no three. The other two aims as
       stated under the introduction section especially no 1 will be additional benefits
       from the study.
   1b. We have modified the study aims according to reviewer’s suggestions as
       follows: (Introduction section, last paragraph): “1) to compare district-specific
       estimates of the IMR (including neonatal and post-neonatal components) and, to
       the extent feasible, their variation over time;
       2) to evaluate determinants of infant mortality, and, in particular, the impact of
       maternal age on the IMRs’ differences between the two districts.”

2. Are the methods appropriate and well described?
   • The study design is not stated. Retrospective is not a study design. This study
     is a retrospective cross-sectional study I presume..
2. We respectfully disagree with the reviewer: this is a retrospective follow up design study, according to the nature of mortality data such as infant mortality. We have modified the title as follows: “Maternal age and Infant Mortality in two Sicilian districts: a retrospective follow up study.”

3. Are the data sound?
   • The data need to be double checked by a statistician.

3. Dataset and output analysis are available on request. One of the authors (MM) has extensive experience in the design and analysis of epidemiologic studies and has closely collaborated with the first author in the analysis of the data.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   • The neither the eligibility criteria nor the outcomes of interest were clearly stated prior to commencement of the study thus introducing selection bias and weakening the focus of the study.

4a. Answering to a comment of a previous reviewer, We have reported the changes to the text, clarifying the criteria used to define the population of infant deaths and the additional information gathered from records pertaining to the admission closest to the time of death.

4b. The 1st paragraph under the result section is confusing and should be clarified

We have modified the text as follows: (Results section, first paragraph) “Two hundred eighty six infant deaths identified by the two ReNCaMs during the period 2004-2006 (Palermo: N=182, Messina: N=104) have been reviewed (Figure 1).”

4c. • Table 1 is very busy and also confusing. It is not clear what the p-values represent. All the tables should be represented in the standard way recommended for most journals.

4c. We have modified the table.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   • The discussion section is limited. There is insufficient reference to previous published local or regional data. Same observation was made regarding the introduction. Therefore the justification for the study was not strengthened by clarifying reports if any on existing literature.

5. Although comparisons of infant mortality rates in specific geographic areas are commonplace in public health agencies in Italy, to our knowledge this is the first
study that systematically evaluates potential reasons for the difference in infant mortality between two distinct areas of Sicily.

6. Are limitations of the work clearly stated?
   • The limitations are stated but there are other methodological flaws that have been pointed out.

6. We have tried to address all comments by all reviewers and we hope that the changes we made are satisfactory.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   • Although the introduction section of the main manuscripts acknowledges previous studies, several statements of facts are not referenced. Reference 8-10 has some typo? error.

7. We have checked the references and they seem to be Ok. Please let us know if error messages appear again.

7b. It is not clear under the introduction and discussion sections whether there have been published literature on this question under investigation in these two regions or whether this is the 1st published work in which a case the dearth of evidence should be clearly stated as justification for the study.

7b. To our knowledge, this is the first scientific manuscript that reports a comparison of two Sicilian districts with respect to infant mortality rates.

8. Do the title and abstract accurately convey what has been found?
   The title does not capture the main thrust of the study, which is to explore aspects of determinants of infant mortality especially maternal age in two Sicilian districts. The purpose of the study is different under the abstract and the main manuscript, albeit more focused in the abstract.

8. We have modified the title and the abstract as written in answers to comment no. 1 and 2.

9. Is the writing acceptable? Basically it is but needs to consider the comments/suggestions made.
   I would consider these recommendations compulsory as they will help to enhance the quality of the manuscript.

Christy Okoromah
Introduction
1. Authors may remove the first objective. The third objective needs to be revised. For example, it will read better if stated as "To assess determinants of infant mortality ......."

1. We have modified the study aims described in the introduction, according to reviewer’s suggestions as follows: (Introduction section, last paragraph): "1) to compare district-specific estimates of the IMR (including neonatal and post-neonatal components) and, to the extent feasible, their variation over time; 2) to evaluate determinants of infant mortality, and, in particular, the impact of maternal age on the IMRs’ differences between the two districts."

Methods
1. Authors seem to have mistaken neonatal mortality rate (NMR) for perinatal mortality rate (PMR). Post-neonatal mortality rate will be deaths of infants occurring after the first 28 days.

1. Whereas we used the standard definition (death in the first 28 days of life) in computing the NMR, and other parts of the data analysis, we incorrectly defined neonatal death in the methods section. We have changed the text to reflect the correct (Statistical methods section, line 2) “For each district and year, IMRs were computed by dividing the number of infant deaths by the number of infants born alive, and multiplying the result by 1000. Similarly, NMR (death occurred in the first 28 days of life) and post-neonatal MR (after the first 28 days of life) were
computed by restricting the numerator to the appropriate interval and dividing by the same denominator."

**Results**

1. Authors reported the Poisson regression model to be significant at $p = 0.05$. What is the cut off point for statistical significance?

The interaction test documented a statistical significance (p-value= 0.04): we have inserted the resulted p-value both in the abstract and in the main text.

2. Authors used Odds Ratio and Risk ratio (not Rate ratio!) in this study. By convention, it is customary to use one estimate of effect. Please utilize only one estimate of effect throughout the report i.e. either Odds Ratio (OR) or Risk Ratio (RR).

2. We use the measure of association that seems most appropriate for the data at hand: the odds ratio is appropriate for comparing deceased infants of the two districts with respect to sociodemographic characteristics and other potential determinants of mortality; we use the mortality rate ratio to compare mortality rates. We disagree with the reviewer's definition of the IMR as a "risk," because the numerator of the IMR is typically not included in the denominator: the infants who die in one calendar year within 12 months of their birth date may have been born in the previous calendar year. We have followed the time-honored tradition of calling the statistic a "rate," on the assumption that the denominator is a valid estimate of the number of infants who are at risk of dying within twelve months of their birth date at any point in the interval, thus approximating a person-time estimate.

We have modified the text as follows: (Results section, forth paragraph): “The ratio of the two district-specific IMRs (RR) was 1.63 (95%CI: 1.25 – 2.09), higher for the neonatal component (RR: 1.82; 95%CI: 1.36 – 2.45) than for the post-neonatal (RR: 1.15; 95% CI: 0.68 – 1.93), indicating higher mortality in the Messina district.”

**Discretionary Revisions**

**Methods**

1. Page 6. The statement ‘The ReNCaMs of Palermo and Messina identified all deaths during the first year of life……..in 2004-2006’ is ambiguous. Perhaps Authors meant to report that ‘We identified all deaths in ReNCaMs of Palermo and Messina ………’

1. The text was modified as suggested: (Methods section, second paragraph) “We have identified in Death Causes Registries of Palermo and Messina all deaths during the first year of life recorded among infants born to residents in 2004-2006.”
Results
1. Authors should include the standard deviation whenever mean values or averages are reported.

1. The tables do not report any mean values that would require S.D. estimates. Most numbers are either percent values, or IMRs and other measures of association. We report 95% CIs when appropriate to provide a measure of precision, but believe that reporting CIs for all point estimates is unnecessary and could compromise the readability of the table.

2. 95% Confidence Interval is usually abbreviated as 95% CI.

2. The text has been corrected.

3. Authors should standardize the number of decimal points. Please use either one or two decimal points consistently in the manuscript.

The text and the table were modified, using one decimal point.

References
Authors should ensure that references conform to Journal style. Please use standard journal abbreviations for journal names.

Checked and revised.

Minor Essential revisions
Introduction/Methods
1. First paragraph. Review reference [8(m) – 10].

1. Checked and revised.

2. Health for All, 2009. Is this a reference?
Revised.

3. The phrase ‘pregnancy health care system’ may be replaced with ‘organization of antenatal care’.

3. We have provided to correct as follows: (Introduction, line 20): "The two districts, compared each other, present differences in demographic and geographical setting, as well as in local organization in term of medically assisted conception (MAC) centres and of birth delivery centres."

4. Authors may express the term ‘largest latitudinal area’ differently.

4. We have eliminated the sentence, having implemented the methods section.

5. The term decedents may be replaced by ‘infants’ or ‘dead infants’ or
‘deceased infants’

5. The term decedents have been replaced along the text as suggested

Results
1. Authors may wish to write 286 in words.
   1. Revised.

2. The first sentence of the third paragraph is not clear i.e. ‘The IMR ratio was 1.63 (95% CI: 1.25 – 2.09), ……..
   2. Revised.

Discussion
1. ‘Malformation related to deaths’ may be changed to ‘malformation-related deaths’.
   1. Revised.

2. The last sentence on the first page of Discussion could be revised particularly the use of the word ‘determined’.
   2. The phrase was modified as follows (first page discussion, last paragraph):
      “Demographic trends in industrialized countries are characterized by a progressive increase in newborns from advanced age mothers, with an increasing number of births related to medically assisted procreation, including assisted reproductive technology”
   3. Change the term ‘assisted procreation’ to ‘assisted conception’.
   3. Revised.

Acknowledgements
Review the first sentence.
Revised.

Table 2
Change cerebrum-vascular to cerebro-vascular.
Revised.

Figure 1
Review and ensure that all boxes are fully written
Revised.