

Title

MONOGRAFIA POPOLAZIONI FRAGILI. Barbara Pacelli's legacy and initial plans for a large-scale investigation into the chronic health effects of earthquakes in Italy

Titolo

MONOGRAFIA POPOLAZIONI FRAGILI. Dal lascito scientifico di Barbara Pacelli: progetto iniziale per uno studio su vasta scala degli effetti cronici dei terremoti in Italia

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1 Abstract

2 Barbara Pacelli, a young Italian epidemiologist, passed away unexpectedly in September
3 2019. During her prolific life, she gave several scientific contributions to natural disaster
4 epidemiology, particularly in relation to the medium and long-term health effects of
5 earthquakes. In this opinion paper, we reflect on Barbara's legacy and outline potential
6 actions that could arise from her work. Particularly, availability of electronic health records
7 would enable a systematic and large-scale investigation into the long-term health effects of
8 earthquakes in Italy, a country with high seismic risk. This effort would have high societal
9 value as it would likely enable mitigation of substantial morbidity and mortality in areas
10 affected by earthquakes. In this paper we define the scope, objectives, potential data sources
11 and analysis methods that could be utilised to systematically assess the chronic health effects
12 of recent earthquakes in Italy.

13 Keywords

14 Obituary, earthquakes, chronic diseases, electronic health records, retrospective cohort, case
15 crossover study

16

17 Riassunto

18 Barbara Pacelli, una giovane epidemiologa italiana, è scomparsa improvvisamente nel
19 settembre 2019. Durante la sua prolifica vita professionale, Barbara ha dato parecchi
20 contributi all'epidemiologia dei disastri naturali, in particolare riguardo gli effetti a medio e
21 lungo termine dei terremoti. In questo *opinion paper*, riflettiamo su un segmento del lascito
22 scientifico di Barbara e delineiamo potenziali azioni che potrebbero derivare dal suo lavoro.
23 In particolare, la disponibilità di dati sanitari elettronici rende oggi possibile uno studio
24 sistematico e su larga scala degli effetti a lungo termine dei terremoti in Italia, un Paese ad
25 alto rischio sismico. Questa iniziativa avrebbe un alto valore sociale in quanto potrebbe
26 consentire la riduzione di una notevole quota di morbilità e mortalità nelle zone affette dai
27 terremoti. Nell'articolo definiamo l'ambito di azione, gli obiettivi, le potenziali fonti di dati e i
28 metodi di analisi che si potrebbero utilizzare per valutare sistematicamente gli effetti cronici
29 dei terremoti avvenuti negli ultimi anni in Italia.

30 Parole chiave

31 Necrologio, terremoti, malattie croniche, dati sanitari elettronici, coorte retrospettiva, studio
32 case crossover

1 Barbara Pacelli's contribution to earthquake epidemiology

2 Barbara Pacelli was a talented epidemiologist, a good friend, and a very active member of the
3 Italian Association of Epidemiology. She served as a board member of the Association
4 between 2014-2016, and those of us who were in the same board distinctly remember her
5 exceptional professionalism and kindness. Besides being unusually skilled, Barbara strove to
6 put her in-depth knowledge of epidemiology at the service of society. At the time of her
7 passing, she already had more than 15 years' experience in the field of environmental and
8 health-inequality epidemiology. In the past few years, Barbara also gave several scientific
9 contributions on earthquake epidemiology. In Italy, a nation with high seismic risk, this
10 commitment has high societal value as it aims at a reduction of morbidity and mortality
11 amongst the most vulnerable strata of the population. In the aftermath of earthquakes,
12 assessing the short-term effects of earthquakes is usually prioritized, because a quantification
13 of casualties and deaths is essential to organise the immediate response. Barbara's
14 contribution focused on the long-term effects, an aspect that is still relatively neglected and
15 that is crucial to ensure that the most vulnerable, such as those who were displaced by the
16 earthquakes or had pre-existing medical conditions, are adequately shielded from the
17 indirect, long-term consequences of earthquakes.

18 As a board member of the Italian Association of Epidemiology, Barbara liaised with local
19 authorities, academics and public health professionals to raise awareness about the
20 scarceness of investigations about the long-term consequences of earthquakes. This advocacy
21 work was conducted with particular interest for L'Aquila earthquake, a major seismic event
22 that occurred in central Italy in 2009 and cost the lives of 308 people and the displacement of
23 several thousands. These initiatives culminated in a well-attended spring meeting of the
24 Italian Association of Epidemiology held in L'Aquila in April 2016, which Barbara contributed
25 to organising and moderating. Barbara also contributed to assembling an open-access
26 monographic issue of the Association's journal, *Epidemiologia & Prevenzione*, in which
27 Barbara co-authored 3 papers.¹⁻³ In this monographic issue, which is available at
28 <https://www.epiprev.it/pubblicazione/epidemiol-prev-2016-40-2-suppl-1>, Barbara's main
29 paper focused on a systematic comparison between studies assessing the long-term health
30 effects of the L'Aquila earthquake and studies assessing other major seismic events. This
31 review found that the L'Aquila earthquake was the most investigated (along with the
32 Kobe/Hanshin- Awaji earthquake, occurred in 1995 in Japan) and its effects were estimated
33 mostly in terms of mental health outcomes. These findings suggested that there was scope
34 for a more comprehensive investigation into the long-term health effects in L'Aquila by using
35 electronic health records, which would have enabled more in-depth assessment of its health
36 effects. However, at the time, a meta-analysis of long-term earthquake effects had not yet
37 been conducted, and therefore the relevance of this kind of new investigation was not yet
38 clear.

39 Barbara was instrumental, together with her co-lead author (Dr Alba Ripoll-Gallardo) and
40 other investigators, to ensure that this initial review was expanded to include a meta-analysis
41 of published studies on long-term health effects of earthquakes in affluent countries. In 2018,
42 this expanded work was published in the *International Journal of Epidemiology*⁴ and an

1 extract was posted on the journal's blog.⁵ This meta-analysis of 52 studies showed that
2 populations exposed to one of 13 major earthquakes (occurred in 8 countries between 1980
3 and 2011) had on average 36% and 37% higher mortality rate for myocardial infarction and
4 stroke after the first month from the main shock, as well as higher mean concentration of
5 glycated haemoglobin. Several other long-term effects were found in relation to psychiatric
6 disorders and other chronic diseases. This work suggested that a new systematic investigation
7 into the long-term effects in Italy would not only be scientifically innovative, but also essential
8 to reduce a preventable and sizeable burden of mortality and morbidity.

9 Finally, in a recent editorial, Barbara and others outlined the features required to a such
10 comprehensive investigation into the health effects of earthquakes.⁶ Because Italy is a
11 country at a high seismic risk, establishing a post-earthquake epidemiological study would
12 enable early detection of many deleterious effects and damage mitigation. Barbara and
13 others proposed that this study should (i) capitalise on routinely collected health data,
14 rendering the study relatively inexpensive, (ii) be coordinated centrally by a multidisciplinary
15 team to enable harmonised procedures and analysis, (iii) capture both physical and mental
16 health diseases (iv) consider a follow-up of at least 7 years, based on the effects found in the
17 meta-analysis⁴ and (v) gather sufficient data to enable stratified analysis and identify at-risk
18 subgroups that may need targeted interventions.

19

20 Plans for a large-scale study into the chronic health effects of 21 earthquakes in Italy

22 Barbara's and others' work has been crucial to reliably formulate the rationale and outline
23 the features of a comprehensive study of the medium and long-term effects of earthquakes
24 in Italy.^{1-4,6-8} We think that it is now time to continue this work and devise the research plan
25 for an investigation into the subject. On average, Italy experienced a major earthquake every
26 three years in the past ten years. Taken together, the L'Aquila (2009), Emilia (2012) and
27 Amatrice (2016) earthquakes resulted in 679 deaths, displacement of more than 120,000
28 people and cumulative economic losses of more than 20 billion euros.⁹ However, their
29 medium and long-term health effects are largely unknown. A comprehensive and rigorous
30 investigation is long-overdue and crucial to ensure that at-risk populations will be adequately
31 protected in the event of a future disaster. In addition to having high public health value, this
32 study would be highly innovative, as a systematic investigation of the health effects of
33 earthquakes has never been performed. Finally, using a large-scale approach (i.e. including
34 the whole population of individuals likely exposed to the earthquake of interest and matching
35 controls) would enable detection of small effects and assessment of potential interactions
36 between earthquakes and socio-demographic characteristics such as age and socioeconomic
37 status; thus enabling greater precision in mitigation and prevention measures.

38

39 Objectives

40 This study will have two main objectives:

- 1 1. to ascertain the medium and long-term effects of earthquakes on pre-specified
2 endpoints;
3 2. to conduct exploratory analyses to capture additional health effects (e.g. arising from
4 an agnostic, phenome-wide association study into the health effects of earthquakes)
5 and interactions with relevant subgroups (e.g. defined by age and socioeconomic
6 status).

7

8 Endpoints

9 Based on previous evidence,⁴ we will consider the following endpoints: (i) all-cause mortality,
10 (ii) cardiometabolic disease incidence and mortality (i.e. coronary heart disease, stroke,
11 diabetes and subtypes), (iii) psychiatric disorder incidence and mortality (i.e. intentional self-
12 harm, major depression, psychotic events), (iv) gastro-enterological disease incidence and
13 mortality (i.e. gastric ulcers).

14

15 Participants

16 To ensure adequate power, the study should gather data from:

- 17 1. Populations exposed to recent major earthquakes in Italy (~2.7 million people)
- 18 1. L'Aquila, 6 April 2009. The province most exposed was L'Aquila (309,131
19 individuals)¹⁰
- 20 2. Emilia, 20 May 2012. The provinces most exposed were Modena (685,822) and
21 Ferrara (352,856)¹¹
- 22 3. Amatrice, 24 August 2016. The provinces most exposed were Rieti (158,467),
23 Ascoli-Piceno (210,066), Perugia (662,110), Teramo (310,339)¹²
- 24 2. Populations unexposed to earthquakes. Control Italian provinces will be selected
25 amongst those that were not exposed to major natural disasters in the previous 20
26 years and will be matched to exposed provinces based on their (i) size, (ii)
27 sociodemographic characteristics (proportion of men and women, people with ≥65
28 years, sociodemographic status, population density), (iii) prevalence of behavioural
29 risk factors (smoking, alcohol drinking, obesity) and (iv) indicators of healthcare quality
30 and efficiency measured before the earthquake of interest. This approach is expected
31 to ensure that exposed and unexposed areas are as balanced as possible in terms of a
32 range of baseline covariates.

33 An anticipated sample size of ~5 million participants from exposed and unexposed provinces
34 will enable an unparalleled range of analyses, including (i) ascertainment of potential
35 subgroup effects that would enable more tailored and efficient public health intervention and
36 (ii) an agnostic investigation of smaller (and therefore previously undetected) associations.

37

1 Proposed study design

2 A retrospective cohort design would enable detailed ascertainment of the effects of
3 earthquakes whilst including individuals who moved beyond their usual residential province.
4 As several thousand people were displaced due to earthquakes, requesting electronic health
5 records only from the exposed provinces would likely result in right censoring of the data,
6 which would bias associations towards the null and therefore lead to likely underestimation
7 of earthquake effects.

8 The proposed design requires (i) individual-level data of the resident population to collect
9 sociodemographic composition of the at-risk population and matched controls before each
10 earthquake, (ii) subsequent linkage with electronic health records and, potentially, (iii) linkage
11 with individual building characteristics to assess potential effect modification.

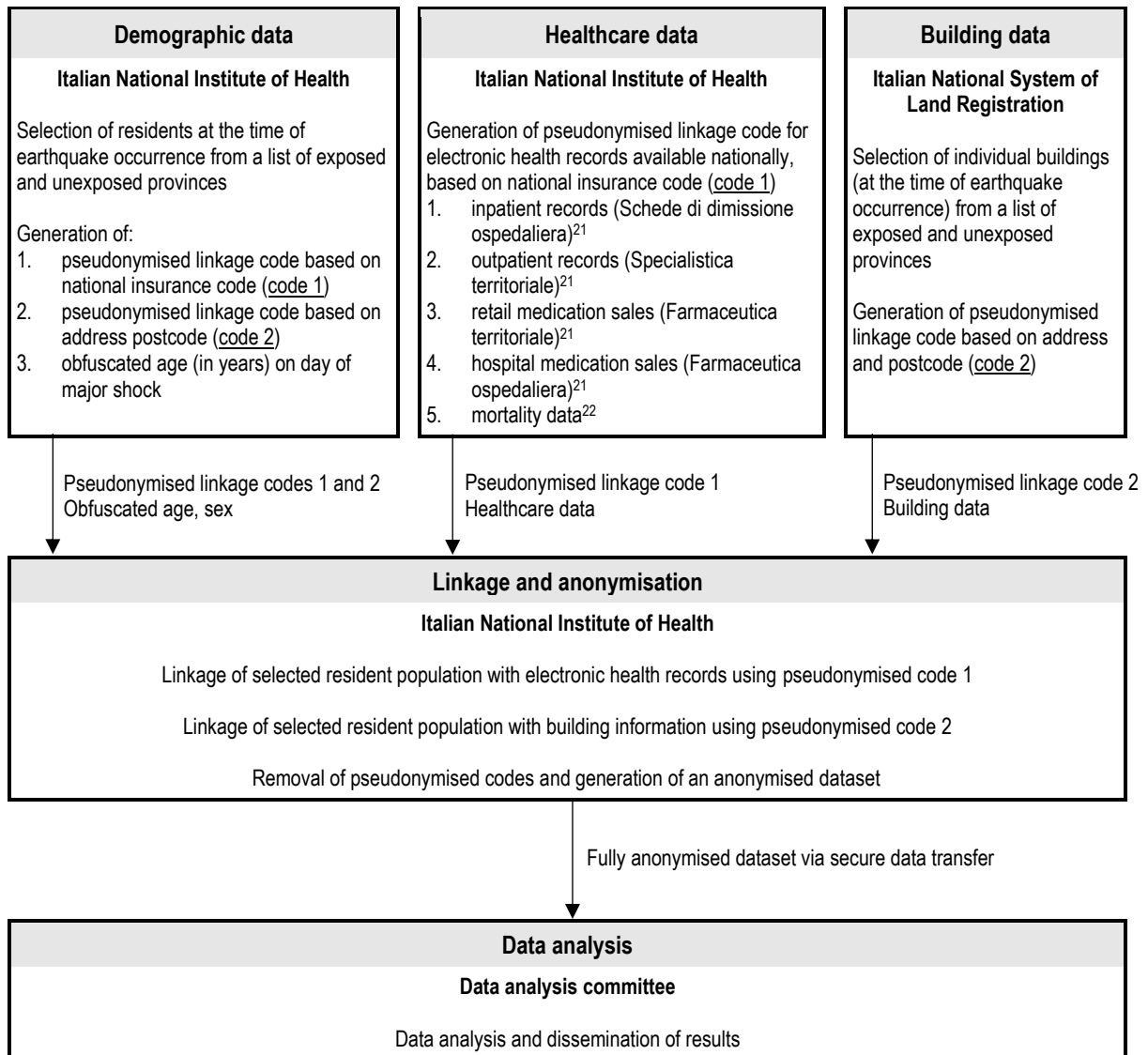
12 A cohort design in disaster epidemiology is not new,¹³ but the idea of linking resident data
13 with e-health data and building characteristics is novel and particularly attractive when
14 investigating the health effects of earthquakes. While building characteristics are known to
15 have an impact on earthquake-related immediate injury and death,¹⁴⁻¹⁷ their impact on
16 chronic health outcomes is unclear. It is possible that living in at-risk buildings may indirectly
17 increase long-term morbidity and mortality, for example via an increased duration of
18 displacement. A better understanding of the potential effect modification arising from
19 building characteristics might further support the need for preparedness efforts related to
20 building-related risk factors. In line with the information analysed in previous short-term
21 studies, building characteristics should comprise essential features that may affect the
22 building's response to seismic shocks, such as configuration (e.g. single building or storey),
23 frame (e.g. reinforced concrete or stones/bricks), and period of construction.¹⁴⁻¹⁷ At the time
24 of writing, it is not yet clear whether individual building characteristics data will be available
25 from the Italian National System of Land Registration (Catasto). If confidentiality concerns
26 render such a linkage difficult, a possible solution could consist in obfuscating building
27 characteristics (e.g. by categorising building construction year) or in generating area-level,
28 aggregated datasets. The latter approach, while practical, has however the disadvantage of
29 being prone to bias due to potential contextual effects of neighbourhood environments on
30 health outcomes (independent of individual building characteristics). Disagreement between
31 individual and area-level socioeconomic status has been shown in previous publications,¹⁸⁻²⁰
32 and it is possible that a similar distortion might occur when using aggregated data of building
33 characteristics.

34 Further details about the proposed linkage process is available in **Figure 1**.

35

36

1 **Figure 1.** Proposed linkage procedures for a retrospective cohort study of the long-term
 2 health effects of recent earthquakes in Italy



3

4

5 An important requirement is that the linkage of individual-level data should occur while
 6 preserving the confidentiality of participants. As such, measures will be applied to
 7 pseudonymise participant information and retain only the data that is essential for analysis
 8 (e.g. after linkage, day of birth and death could be obfuscated to prevent re-identification).
 9 We feel that, ideally, this process should be managed by the Italian National Institute of
 10 Health (Istituto Superiore di Sanità). The purpose of this study would fall within their
 11 institutional mission to protect national public health, as reflected by their previous
 12 involvement in studies assessing the health impact of the L’Aquila earthquake.²³⁻²⁶
 13 Furthermore, the Italian National Institute of Health have access to demographic and
 14 healthcare data needed for this study, which would likely facilitate generation of an
 15 anonymised analytic dataset. However, alternative options should be explored if this solution
 16 is not viable. For example, investigators could consider a decentralised approach similar to

1 the one used in a large-scale investigation of factors associated with COVID-19 prognosis in
2 17 million UK participants.²⁷ In this approach, a standardised software would be provided to
3 regional authorities which would perform linkage and analyses locally, and only summary
4 association statistics are shared with the data analysis committee. This method would likely
5 reduce confidentiality problems but would have the disadvantage of not enabling linkage of
6 participants that used healthcare facilities outside of their region of residence.

7

8 [Alternative study design](#)

9 If the design described above is not feasible, e.g. due to the difficulty in linking resident data
10 with healthcare data and building characteristics, we will only request anonymised healthcare
11 data from provinces exposed and unexposed to earthquakes (as defined in the 'Participants'
12 paragraph). This will enable quantification of disease events and deaths occurred both before
13 and after the earthquake in exposed provinces and in matched unexposed provinces.

14 While this approach does not need linkage with demographic data, it is worth noting that due
15 to the high numbers of displaced people, a sizeable proportion of participants will likely not
16 be captured by electronics health records. This unfortunately might bias associations towards
17 the null due to right censoring, thus underestimating earthquake effects.

18

19 [Investigation into potential intermediate traits](#)

20 As a complement, a parallel study could be conducted analysing variation in risk behaviours
21 from the 'PASSI' national surveillance, active since 2006.²⁸ In the meta-analysis that Barbara
22 co-led, a two-fold increase in sedentary behaviour was noted, suggesting that a thorough
23 investigation into behavioural determinants of health and intermediate traits of
24 cardiometabolic diseases would be useful to complement analyses on health outcomes.

25

26 [Additional exploratory analyses](#)

27 Given its large scale, we envision that this study should also attempt to assess the effects of
28 earthquakes on all outcomes available from electronic health records via a phenome-wide,
29 agnostic assessment (while conducting appropriate adjustment for potential false-discovery
30 rate). Ideally, this study should also attempt investigation of potential subgroup effects by
31 sociodemographic characteristics (e.g. sex, age, socioeconomic status) and geographical
32 region (as some heterogeneity in damage and damage mitigation is expected owing to broad
33 socioeconomic inequalities).

34

35 [Public engagement and involvement](#)

36 Using electronic health records for public health research is within the scope of the General
37 Data Protection Regulation (GDPR) (EU Regulation 2016/679), which in Articles 6(1) and 9(2)
38 allows data processing in the public interest and for scientific research purposes.²⁹

1 We feel that it would be useful to be transparent about this plan and confer with the general
2 public, including (but not limited to) associations of earthquake victims and their relatives.
3 This will hopefully ensure that the purposes and methods of this study are aligned with the
4 public's priorities and expectations.

5 Conclusion

6 In this opinion paper, we summarised the contributions to earthquake epidemiology by
7 Barbara Pacelli, a talented epidemiologist who passed away unexpectedly last year. Based on
8 her work, we feel that there is a strong rationale for a large-scale investigation into the long-
9 term health effects of earthquakes in Italy. We propose a retrospective cohort study design
10 that would enable follow-up of displaced populations, thus resulting in reliable estimation of
11 earthquake effects. The investigation will be led by a consortium of centres with expertise in
12 disaster medicine and preparedness (CRIMEDIM WHO Collaborating Centre, Italy),
13 earthquake epidemiology (University of L'Aquila, Italy), and analysis of large-scale datasets
14 (University of Cambridge, UK). If successful, this effort would be the first to reliably assess the
15 long-term health effects of earthquakes at an unprecedented scale and detail.

16

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22

23 Conflict of interest statement

24 The authors declare that they have no conflict of interest.

25

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