*Title Page

The health of communities living in geothermal areas: a review.

Elisa Bustaffa[*,1], Liliana Cori[1], Adele Manzella[2], Daniela Nuvolone[3], Fabrizio Minichilli[1], Fabrizio Bianchi[1], Francesca Gorini[1]

[*]Corresponding author

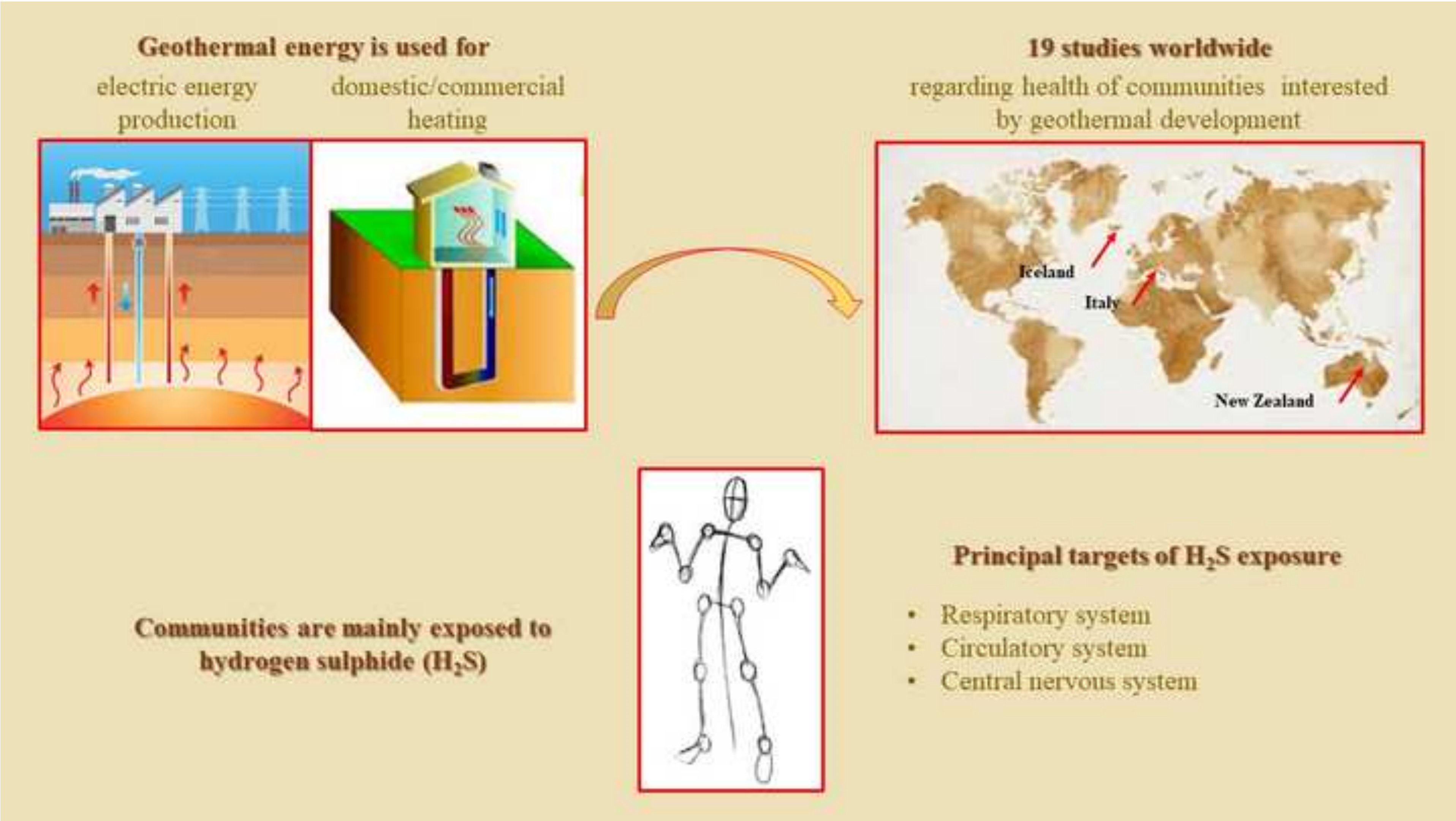
E-mail address: elisa.bustaffa@ifc.cnr.it (E. Bustaffa).

[1] Unit of Environmental Epidemiology and Diseases Registries, Institute of Clinical Physiology, National Research Council, IFC-CNR, via Moruzzi 1, Pisa 56124, Italy

[2] Institute of Geosciences and Earth Resources, National Research Council, IGG-CNR, via Moruzzi 1, Pisa 56124, Italy

[3] Epidemiology Unit, Regional Health Agency of Tuscany, Via Pietro Dazzi 1, Florence 50100, Italy

*Graphical Abstract



***Highlights (for review : 3 to 5 bullet points (maximum 85 characters including spaces per bullet point)**

- Communities living in geothermal areas show increased risk for several cancer sites.
- Exposure to hydrogen sulfide emissions are mainly associated to respiratory diseases.
- Other interesting outcomes concern circulatory and nervous system diseases.
- The exposure assessment needs more accuracy and precision.
- An integrated health-environment surveillance system is recommended.

*Manuscript (double-spaced and continuously LINE and PAGE numbered)-for final publication
Click here to view linked References

Key words: geothermal, health, hydrogen sulfide, epidemiology, environment, sustainable energy

Abstract

Background: Since the 1990s, in areas with natural geothermal manifestations studies on the association between exposure to pollutants and health effect have become increasingly relevant. These emissions consist of water vapor mixed with carbon dioxide, hydrogen sulfide (H_2S), methane and, to a lesser extent, rare gases and trace elements in volatile forms.

Objectives: Considering the indications of the World Health Organization and the growth in the use of geothermal energy for energy production, this review aims to report studies exploring the health status of the populations living in areas where geothermal energy is used to produce heat and electricity.

Methods: Studies on the health effects of the general population exposed to emissions from both natural geothermal events and plants using geothermal energy at domestic or commercial level have been considered between 1999-2019. Studies were classified into those based on health indicators and those based on proxy-individual level exposure metrics. Both statistically significant results (p<0.05) and interesting signals were commented.

Results: The 19 studies selected (New Zealand, Iceland and Italy) provide heterogeneous results, with an increased risk for several tumor sites. Exposure to H_2S low concentrations is positively associated with an increment of respiratory symptoms, anti-asthma drugs use, mortality for respiratory diseases and lung cancer. Exposure to H_2S high levels is inversely related to cancer mortality but associated with an increase in hospitalization for respiratory diseases, central nervous system disorders and cardiovascular diseases.

Conclusions: The results indicate that the health of populations residing in areas rich in geothermal emissions presents some critical elements to be explored. The two major limitations of the studies are the ecological design and the inadequate exposure assessment. The authors suggested the prosecution and the systematization of health surveillance and human biomonitoring activities associated with permanent control of atmospheric emissions from both industrial and natural plants.

Abbreviations: As, Arsenic; BCC, Basal Cellc Carcinoma; CAUs, Census Area Units; CNS, Central Nervous System; CO_2, Carbon dioxide; COPD, Chronic Obstructive Pulmonary Diseases; CRA, Cold Reference Area; ED, Emergency Department; EIA, *Environmental Impact Assessment; GHA, Geothermal Heating Area; HD, Heart Disease; HRs, Hazard Ratios; H_2S, Hydrogen sulfide; Hg, Mercury; IEA, Integrated Environmental Authorization; IR%, percentage increases in risk of death; NGA, Northern Geothermal Area; NHL, Non-Hodgkin's Lymphoma; NO_2, Nitrogen Oxide; O_3, Ozone; PM, Particulate Matter; PM_{10}, Particulate Matter with a diameter ≤10 µm; RAEP, Regional Agency for Environmental Protection; RGS, Rotorua Geothermal System; Rn, Radon; SGA, Southern Geothermal Area; SIRs, Standardized Incidence Ratios; SMRs, Standardized Mortality Ratios; TGA, Total Geothermal Area; WHO, World Health Organization; WRA, Warm Reference Area.*

1. Background

Geothermal energy is the thermal energy stored underground, which generates geological phenomena on a planetary scale such as volcanoes, geysers, fumaroles and hot springs (Dickson and Fanelli, 2003; Bustaffa et al, 2017). From an industrial and technological point of view, geothermal energy refers to that portion that can be recovered and used for conversion into energy products. In most cases, geothermal technologies produce thermal and electrical energy extracting hot fluids from hydrothermal reservoirs. Once at the surface, fluids of various temperatures can be used to generate electricity or, more directly, for applications that require thermal energy, namely space heating of buildings, bathing and balneology (spas and swimming pools), horticulture, industrial process heat and agricultural drying (IPCC, 2012; Shortall et al, 2015). Whereas enhanced geothermal system is still in the demonstration and pilot phase, hydrothermal systems have been used for about 100 years to produce electricity from high temperature fluids (essentially above 100°C) and for thermal applications (IPCC, 2012; Shortall et al, 2015). At the last World Geothermal Congress in 2015, 83 countries were reported to be using geothermal energy for thermal uses and 26 countries for producing electricity (Bertani, 2016; Lund and Boyd, 2016). Geothermal energy produces worldwide 73.7 TWh (Terawatthours) of electricity with 12.7 GWe (Gigawatt of electricity) of installed capacity, and 164.6 TWh of heat with an installed capacity of 70.9 GWth (Gigawatt of thermal energy) (Manzella et al, 2019a, 2019b, 2018) contributing for the 0.1% of the global primary energy supply and for the 2% of the total global demand for heat in 2008 (Shortall et al, 2015).

In recent years the interest around geothermal energy has grown all over the world, since geothermal is a renewable source to be utilized for energy transition, to move from a fossil-fuel centralized system towards a more distributed fossil-free system (Manzella et al, 2019a). The issue of reducing the environmental impacts of traditional energy production is crucial. The commitments in this direction were confirmed at the 21st Meeting of the Conference of the Parties of the United Nations Framework Convention on Climate Change in Paris in 2015 (COP21). Additionally, the European Union introduced legal binding instruments to support progresses, in the framework of the 2030 Climate and Energy Package (EU Energy 2030). By 2050 geothermal production is estimated to account for 3% of the global electricity demand and 5% of the global demand for heating and cooling (IPCC, 2012). In Europe alone the geothermal market should experience a trend doubling the installed capacity for geothermal electricity between 2010 and 2020, from a total of 816 MWe to 1,627 in 14 countries, and a five-folds growth trend for geothermal heat production, from 568 ktoe (thousands of tons of fossil oil for an equivalent energy production) to 2,630 ktoe in 21 countries in the same period (Dumas, 2019).

Although geothermal energy is generally considered a clean and sustainable energy source, geothermal industrial development produces an impact on the environment (Kristmannsdóttir and Ármannsson, 2003; Shortall et al, 2015; Manzella et al, 2018). Among other effects, effusions from geothermal plants may occur if the produced geothermal fluids contain polluting elements and in case they are not completely contained and treated in order to avoid the contact with air, water and soil. Potential emissions into the air include carbon dioxide CO_2, hydrogen sulfide (H_2S), hydrogen, ammonia and methane, radon (Rn), volatile metals, silicates, carbonates, metal sulfides and sulfates and traces of mercury (Hg), arsenic (As), antimony, selenium and chromium (Bravi and Basosi, 2014; Shortall et al, 2015). Potential contaminants of geothermal water include chlorides and sulfides or metals (aluminum, boron, As, cadmium, lead, lithium, iron, Hg, zinc, and manganese) (Kristmannsdóttir and Ármannsson, 2003; Shortall et al, 2015). In fluids containing non condensable gases, CO_2 is the most abundant and its emission from some geothermal electricity plants is not negligible (Ármannsson et al, 2005). However, H_2S emission is, the one probably causing the greatest concern due to its unpleasant smell and toxicity in moderate concentrations (Kristmannsdóttir and Ármannsson, 2003). Approximately 90% of the total emitted H_2S comes from natural sources such as swamps, bogs, sulfur springs and volcanoes, though it can also be released from human-made processes including natural gas, petrochemical and geothermal plants, municipal sewers and sewage treatment plants, tanneries (WHO, 2000; ATSDR, 2016). The exploration of the health problems derived from the use of geothermal fluids has begun after a publication in 1981 by the World Health Organization (WHO) Task Group on Environmental Health Criteria for Hydrogen sulphide recommending that *"...studies should be initiated among the general population in a geothermal area, taking advantage of the natural conditions provided, for example, by the situation in Rotorua, New Zealand*" (IPCS, 1981).

Considering the early warning from WHO and the growth of geothermal energy industrial development for the coming years (Manzella, 2019a), in this review the authors report the studies exploring the health status of populations residing in areas where geothermal fluids rich of H_2S and other contaminants are used to produce heat and electricity. This is presented and discussed to support the identification of evidence-based methodologies for health impact assessment in geothermal industrial development, required in the framework of environmental impact assessment (EIA) procedures developed for new installations or integrated environmental authorization (IEA) for existing plants.

2. Material and methods

2.1. Search criteria

The search was restricted to articles published in English considering only peer-reviewed original articles selected in PubMed for the period 1990-2019 and using as search terms (("geothermal" OR "geothermics") AND ("health")). Only original studies on health effects on the general population exposed to emissions from geothermal plants or from facilities that convey geothermal fluids for domestic use were included. Consequently, occupational studies, studies on thermal waters, studies on exposure assessment and on environmental monitoring, studies concerning the health effects of volcanic emissions (in addition to the geothermal ones) were excluded. Results were reported classifying studies into two categories: ecological studies based on health indicators and analytical studies that also consider proxy-level exposure measures at the individual level. Within each of these categories, given the characteristics of the areas involved (New Zealand, Iceland, Italy), as described in the following paragraphs, results were reported separately by geographical area. All the statistically significant results ($p<0.05$) were reported and discussed, considering results obtained after adjusting for confounding factors, as well as those that provided interesting signals even though did not reach statistical significance. Furthermore, given the heterogeneity of the three areas on which the studies are based, in the following paragraphs a characterization of these areas is provided.

2.2. Characterization of the areas

2.2.1. New Zealand

The Rotorua area has been considered a particularly useful place to investigate long-term effects of H_2S (IPCS, 1981). The Rotorua Geothermal System (RGS) is one of the 12 natural geothermal systems located in the Bay of Plenty Region and it is a byproduct of volcanic activity in the Taupō Volcanic Zone whose geological landscape is dominated by 8 calderas (Scott, 2019). The RGS occupies ∼25 km^2 in the southern part of one of these 8 calderas on the shore of an 80 km^2 lake (Durand and Scott, 2005). Natural surface features of the RGS include rare geysers, boiling springs, hot pools, fumaroles, barren, and unvegetated warm ground. These features are concentrated either within or directly adjacent to the urban area of Rotorua (about 61,000 inhabitants). Rotorua City may be considered the largest population center in the world whose central business district and surrounding suburbs are built over an actively degassing geothermal field (Durand and Scott, 2005, 2003), which is exclusively used for domestic/commercial purpose, not for the electricity energy production with the consequent absence of geothermal electricity plants (Scott, 2019). The Rotorua area has been inhabited for centuries by the Maori people and, since the 19th century, by European immigrants, who used it as spa. Nowadays, in Rotorua the geothermal fluid is directly used for bathing and wellness, including commercial properties and private use. Space and water heating accounts for a significant proportion of the use, including commercial properties, the Rotorua Hospital and municipal facilities. Over 400 homes are heated by geothermal energy in Rotorua. Rotorua is characterized by the typical "rotten-egg" H_2S odor emitted by vents located in and around the city. In fact, the RGS can be considered as a low sulfidation system, which reduces almost all magmatic SO_2 to H_2S (Giggenbach, 1997) responsible of the considerable nuisance air pollution in Rotorua. Ambient levels of geothermal emissions are heterogeneous across the city and passive samplers have been placed at spaced locations around the city and left for specified periods of time during both winter and summer months in order to map H_2S variations (Horwell, 1998). Not all residents are equally exposed, as the main emissions sources of H_2S are along a line that stretches from the Whakarewarewa geothermal area (a popular tourist area), to Lake Rotorua (an old volcanic caldera). Extensive monitoring surveys regularly performed during the past several years in the geothermal area of Rotorua, showed that around a quarter of the population was regularly exposed to H_2S concentrations exceeding 200 µg/m^3 (143 ppb) (Fisher, 1999; Bates et al. 2002). The highest concentrations measured exceeded 1,500 µg/m^3 (1,000 ppb) (Fisher, 1999). Based on the results obtained from the network of samplers suitably installed for the study of Horwell et al. (2005), Rotorua area can be divided into three zones of H_2S concentration: a high central corridor always affected by the highest H_2S concentration (~1 ppm), a low concentration area in the west of the city (0-40 ppb), that is rarely affected by more than background levels of H_2S, and a medium concentration area in the east of the city, characterized by the central corridor depending on wind direction (500 ppb) (Horwell et al, 2005).

Due to its large exposed population, Rotorua has particular advantages as a place to study possible H_2S effects because there are no co-emitted gases that might confound any findings, being other emissions mostly composed by CO_2 and water vapor (Bates et al, 2017).

2.2.2. Iceland

Geologically, Iceland is a young volcanic island located in the North Atlantic Ocean on the boundary between the North American and Eurasian tectonic plates. These two plates are moving apart at a rate of about 2 cm per year and Iceland is an anomalous part of the ridge where deep mantle material wells up and creates a hot spot of unusually great volcanic productivity and several geothermal fields, emerging as an island (Fridleifsson, 1979; Saemundsson, 1979). The central part of the island, where the ridge is located, has a younger bedrock and the most active volcanic features and emission centers, Iceland, with a total population at 1 January 2019 of 339,589 inhabitants, is one of the countries with the lowest population density in the world; almost two thirds of the population live in the capital (http://worldpopulationreview.com/countries/iceland-population/). In Iceland geothermal water and steam have been used for decades for domestic heating, bathing and showering, and in various industries (Fridleifsson, 1979; Saemundsson, 1979). The geothermal hot water, extracted from deep drilled wells (down to 800 m), is piped into domestic houses, industries and green houses and used for heating, laundry, bathing, showering and washing dishes but not for drinking water (Haraldsson and Ketilsson, 2010). The geothermal supply distribution systems consist of a network of pipes conducting the water from the boreholes to serve each of the homes and other buildings in the respective community, with few exceptions; the main feeding pipe for the communities can be up to 20 km long (Haraldsson and Ketilsson, 2010). Until early last century, Iceland's geothermal energy was limited to bathing, laundry and cooking, and also at present approximately 90% of all houses and swimming pools are heated with geothermal water (Haraldsson and Ketilsson, 2010). The faint rotten egg odour of H_2S breaking out from showers, spas and swimming pools is frequently perceived by foreign visitors, while the local population seems to have acclimatized the smell. Thermal uses are still significant but after space heating (43% of the utilization of geothermal energy), electricity generation is one of the most important uses of geothermal energy (40%). Generating electricity with geothermal energy has increased significantly as a result of a rapid expansion in Iceland's energy intensive aluminum industry. The installed generation capacity of geothermal power plants totaled 665 MWe in 2015 and the production was 5,245 GWh (Gigawatt hours) (Bertani, 2016).

Iceland’s capital area (Reykjavík and its surrounding municipalities) is known for being among the cleanest metropolitan areas in the world since there is little industrial pollution and geothermal energy has replaced the use of fossil fuels for house heating. However, when weather conditions in Reykjavik are dry and windy, levels of particulate matter that is less than or equal to 10 µm in diameter (PM_{10}) may increase sharply and even surpass those of much larger European capitals (Jóhannsson, 2007). The main source of particulate matter in Iceland’s capital area is vehicular traffic (UHR, 2007), though the contribution from naturally occurring sandstorms is substantial (Arnalds, 2010). Furthermore, in Iceland, many cars are driven with studded tires, thus eroding the asphalted streets during winter, and per capita car ownership is among the highest in the world (Economist, 2008). The ambient air pollution in Reykjavík is not only due to traffic-related emissions (World Bank Group, 2014). The combined H_2S emissions from the two geothermal power plants ranged from 7,224 tons/year in 2003 to 20,756 tons/year in 2009 (Olafsdottir and Sigurdardottir, 2013). The main contribution to ambient H_2S is from the Hellisheiði power plant, since the Nesjavellir power plant is behind a mountain, which limits the dispersion of H_2S westward in the direction of the capital. Hellisheiði power plant started operation in September 2006.

2.2.3. Italy

All geothermal power plants in operation in Italy are located in the southern part of the Tuscany region, where the geothermal resources proved to be among the most productive in the world (Bertani, 2016). The geothermal fields used for electricity generation are in the areas of Larderello, Travale, Radicondoli, Lago (Northern Geothermal Area, NGA), and Piancastagnaio, Bagnore (Southern Geothermal Area, SGA) (ARPAT, 2015). Sixteen municipalities are included in the geothermal areas, eight in the NGA and eight in the SGA, with an overall population of 41,171 inhabitants in 2019 (ISTAT, 2019).

Geothermal fluids have been used in Larderello for industrial application since the XIX century, initially for the production of boric acid and then to generate electricity: after a first experiment of power production from geothermal fluids on 1904, the first geothermal power plant in the world began the production in 1913 (ARPAT, 2015). Currently, 36 geothermal plants produce 6,064 GWh of electricity, with an installed power of about 915 MW. The contribution of geothermal electricity generation is 2.0% of the whole Italian generation, and covers over 30% of the electricity needs in Tuscany (Manzella et al, 2019b).

Starting from 1997, the regional agency for environmental protection (ARPAT) conducted periodic campaigns on the whole geothermal area, with main attention to the Hg and H_2S gaseous emissions, considered the most representative pollutants of the pressures exerted by the anthropic and/or natural geothermal activities that characterize the territory. H_2S is, after CO_2, the most abundant non condensable gas emitted by geothermal power plants in Tuscany. Metals, including Hg and As, are widespread in the soil of SGA. A significant contribution to their presence is the natural occurrence of Hg and associated minerals due to the past mineral alteration produced by the natural circulation of geothermal fluids at shallow level. The quantity of Hg was so high that it gave rise to the third largest Hg mining district worldwide (Lattanzi et al, 2019). In addition to the natural occurrence, an important role is most probably played by the intense past mining activity, which ended in the early 1980’s and left mining waste that have been only partially removed. Since Hg and As are present in the geothermal fluids, their effusion in the atmosphere and subsequent deposition on the surrounding soils may also play a role, and require monitoring. The public air quality monitoring network for geothermal power plants in Tuscany includes two mobile laboratories, plus a fixed unit (close to Larderello, and belonging to the network of monitoring stations coordinated by regional authorities), which monitors H_2S, ozone (O_3), nitrogen dioxide (NO_2) and PM_{10}. Moreover, H_2S is monitored with 18 air quality fixed units located in NGA and SGA, and managed by the power plants' operator; data from control units are periodically checked, validated and published by ARPAT.

Nowadays, Hg and H_2S emission levels in the geothermal areas amount to 0.002-0.09 μg/m^3 for Hg, and 8-60 μg/m^3 (daily average) and 2-12 μg/m^3 (average for a period of 90 days) for H_2S (ARPAT, 2018). These values are lower than the limit values defined by the WHO, which established 1 μg/m^3 as yearly average limit for Hg, and 150 μg/m^3 (daily average) and 20 μg/m^3 (average over a period of 90 days) as limit for H_2S (WHO, 2000). In the past these values were significantly higher, and were lowered by installing filters for the abatement of H_2S and Hg, with abatement rates of over 90% (Manzella et al, 2018; Nuvolone et al, 2019).

3. Results

The research identified 90 items after the exclusion of 11 reviews, and 19 papers, 9 performed in New Zealand, 7 in Iceland, and 3 in Italy, were included in this review. Although one of the Italian papers had the abstract in English and the text in Italian, it was nevertheless analyzed and commented. As previously written in the "Material and methods" paragraph, results were reported firstly by the defined categories and then for geographical area. Furthermore, in order to make the reading more fluid, all the statistically significant numerical results have been reported in the tables while in the text are also reported interesting signals even if they not reach the statistical significance. Table 1 summarizes results of studies based on health indicators while Table 2 reports main results of studies based on proxy-level exposure metrics at the individual level.

3.1. Studies based on health indicators

3.1.1. New Zealand

The studies performed in this area considered Standardized Mortality Ratios (SMRs) and Standardized Incidence Ratios (SIRs), comparing residents domiciled in the Rotorua territorial local authority area with those living in the rest of New Zealand (Bates et al, 1998, 1997). Because the proportion of Maori in Rotorua is markedly higher than in the rest of New Zealand, authors chose to use a census ethnicity stratification of Maori ethnicity only (sole Maori) and *"other"*. The overall SMR for diseases of the respiratory system was elevated with a particularly high risk for Maori women. For diseases of the circulatory system, *"other"* mortality was lower, especially for men for whom the reduction was statistically significant. Following the adjustment for ethnicity and sex, authors observed significantly elevated SMRs for rheumatic fever and chronic rheumatic heart disease (HD), hypertensive disease, pneumonia and influenza, and chronic obstructive respiratory disease and allied conditions. There was a statistically significant mortality defect for other HD (Bates et al, 1997). Standardized Incidence Ratios (SIRs) were not alarming though Maori women had an elevated risk for neoplasms of the trachea, bronchus and lung (Bates et al, 1998). The major disease groups were also evaluated by subcategories. Despite the limited interpretation due to the small numbers of cases, an elevated rate for the cancer of the bronchus and lung unspecified was detected whereas cancer of the upper lobe, bronchus or lung was associated with a significantly low risk. Regarding hospital discharge data, SIRs were statistically significant for disorders of the peripheral nervous system, other disorders of the central nervous system (CNS), neurological disorders of the eye and adnexa, diseases of arteries, arterioles and capillaries, diseases of veins, and lymphatic and other circulatory diseases or significantly reduced for acute respiratory infections, cerebrovascular disease, diseases of pulmonary circulation (Bates et al, 1998).

When it became possible to classify urban Rotorua census area units (CAUs) by exposure levels to H_2S (high, medium or low), Bates et al. (2002) observed evidence for exposure related trends for diseases of the nervous system and sense organs, of the circulatory system and of the respiratory system. Grouping each cause for minor diseases, evidence of exposure-related trends, particularly for other disorders of CNS, of the eye and adnexa, cerebrovascular disease, diseases of arteries, arterioles and capillaries, and chronic obstructive pulmonary disease (COPD), was found.

As reported in the paragraph 2.2.1., Horwell et al. (2005) mapped the ambient outdoor H_2S showing that the city may be divided into three segments of average H_2S concentrations related spatially to the flux of ground gases and their subsequent advection. Considering both the limitations on the exposure assessment in the studies previously conducted in Rotorua (Bates et al. 2002, 1998, 1997) and the recent ambient outdoor H_2S map (Horwell et al, 2005), Durand and Wilson (2006), explored the rates and the spatial patterns of non-infectious respiratory diseases in Rotorua to evaluate their relationship to H_2S air pollution. Findings from a spatial cluster analysis of 11 years of hospital discharge data at the CAU resolution were reported. Significantly, the CAUs most polluted by H_2S (~1 ppm) were also those containing primary clusters of all diseases of the respiratory system and noninfectious respiratory problems: asthma, COPD collectively, and symptoms involving respiratory system and other chest symptoms, which represented 45% of total hospital admissions for respiratory problems. Relative risk values were relatively high and ranged from 5.1 to 11.8 within these subgroups (p<0.001) suggesting that risk for noninfectious respiratory diseases were significantly higher in areas characterized by elevated H_2S (Durand and Wilson, 2006).

3.1.2. Iceland

Between 2012 and 2016, the four population-based studies conducted in Iceland (Kristbjornsdottir et al, 2016; Kristbjornsdottir and Rafnsson, 2015, 2013, 2012) considered the communities in geothermal heating areas (GHA), most of them located in the central region of the country (bedrock <3.3 million years old) and some were on or near even younger bedrock (<0.8 million years old). Similarly, the two reference populations, who had not utilized geothermal heating systems as old as 1972 (Haraldsson and Ketilsson, 2010), were identified by the community census codes and age of the bedrock (Kristbjornsdottir and Rafnsson, 2015). Thus, the cold reference area (CRA), considered the main comparison population in the studies, included residents of communities located in the west and east parts of Iceland where the bedrock is in the range of 3.3-15 million years old, while warm reference area (WRA) included residents of communities located in the central region of the country where the age of the bedrock is variable but ranging from <0.8 to 15 million years old. Populations living in the area of the capital, Reykjavik, and in the adjacent Reykjanes area were not included in the study, as the population of the capital area and its adjacent south-west peninsula has had higher cancer incidence then the rest of the country in the Cancer Registry since the beginning of the registry (Jonasson and Tryggvadottir, 2012), a well-known phenomenon in cancer registries, sometimes called the capital effect (Doll, 1991).

The first study conducted aimed at exploring whether residence in the GHA, where inhabitants were exposed to geothermal emissions and water containing H_2S and Rn, was associated with risk of cancer (Kristbjornsdottir and Rafnsson, 2012). The study showed an excess for several cancers, cancers of pancreas and breast, non-Hodgkin's lymphoma (NHL) as compared with the WRA and the CRA (Kristbjornsdottir and Rafnsson, 2012). Comparing the GHA to the CRA, the most significant results were the excess of basal cell carcinoma (BCC), breast and bone cancers, and NHL among women and the excess of NHL, BCC and pancreatic cancer among men (Kristbjornsdottir and Rafnsson, 2012). Then, the same authors evaluated whether the previous risks of cancer were associated with the use of geothermal hot water for heating and washing rather than with the location of residence on geothermal soil (Kristbjornsdottir and Rafnsson, 2013). An association between residence in GHA for decades and increased risk for several cancers, BCC, cancers of breast and kidney, cancer of lymphoid and hematopoietic tissue, compared to both the WRA and CRA, was observed (Kristbjornsdottir and Rafnsson, 2013). Consistently with previous results, an evidence of an exposure-response relationship was found, as the hazard ratios (HRs) were higher in the comparison with the CRA than with the WRA. Comparing the GHA to the CRA, the most significant results were the excess of BCC in the total cohort, and the excess of breast cancer, cancer of lymphoid and haematopoietic tissue, BCC and NHL in women and the excess of BCC, and prostate, oesophagus and kidney cancers among men (Kristbjornsdottir and Rafnsson, 2013). The evaluation whether the increased incidence observed was also reflected in cancer mortality among the population in the GHA, showed an increased mortality for breast cancer, and immunoproliferative diseases in women and for prostate cancer and NHL among men (Kristbjornsdottir and Rafnsson, 2015). Given the results obtained so far, Kristbjornsdottir et al. (2016) tried to assess whether cumulative length of residence in a GHA was associated with cancer risk, considering again WRA and CRA. HRs were generally higher in comparison with the CRA than with the WRA, and also when stratified on categories of cumulative years of residence than without such stratification. Specifically, the HRs were increased for all cancers and for several selected cancer sites, including pancreas, breast, prostate, and kidney, and the combined cancers of the lymphoid and haematopoietic tissue, counting NHL, myelodysplastic syndromes and BCC. Results for women and men separately showed a similar pattern as for the sexes combined (Kristbjornsdottir et al, 2016). Overall, a dose-response association can be observed since the risk for cancers sites were more elevated in comparison with the CRA than with the WRA. In addition, when considering cumulative years of residence in the areas, the risk for these cancer sites were generally higher compared with the risk when length of residence was not accounted for, again in a dose-response manner (Kristbjornsdottir et al, 2016).

3.1.3 Italy

The first study was conducted in order to evaluate the health status of population living in Tuscany geothermal areas (Minichilli et al, 2012). The health analysis showed that in both geothermal areas (NGA and SGA) mortality rates steadily declined from 1971 to 2006, in men and women, coherently with the regional data. In the total geothermal area (TGA=NGA+SGA) a statistically significant mortality excess was observed for all causes only among men, using as reference the population residing in neighboring municipalities. The mortality excess among men was more evident for infectious, respiratory and nervous system diseases, and malignant neoplasm of liver and intrahepatic bile ducts. Among women, a significant mortality excess for liver cirrhosis emerged, while mortality for ischemic HD was significantly lower than expected. Results of mortality analysis clearly showed a geographical heterogeneity, being the SGA disadvantaged when compared to the NGA. In the NGA, a significantly decreased mortality for all neoplasms and an excess for infectious diseases were observed among men. In the SGA, mortality picture was more critical, accounting for the majority of the excesses detected in the TGA and considering additional excesses, namely for malignant neoplasms of liver and intrahepatic bile ducts and of trachea, bronchus, and lung in men, and for acute respiratory disease and diseases of the digestive system in women (Minichilli et al, 2012). In the TGA, hospitalization did not show any excess for all causes and all neoplasms in both sexes. On the other hand, statistically significant excesses were found for malignant neoplasm of stomach and of lymphatic and hematopoietic tissue, particularly for leukemia among women, and for diseases of the respiratory system among men. As highlighted by mortality analysis, also hospitalization results showed a worst picture in the SGA than in the NGA. In fact, in the NGA a rise of hospitalization for all causes and leukemia among women and for diseases of the digestive system in both sexes, was detected. In the SGA, unlike what emerged from the results on mortality, no increase of hospital admissions was observed for all causes and neoplasms in both sexes, but an excess of hospitalization was detected for malignant neoplasm of liver and intrahepatic bile ducts in men, for malignant neoplasm of stomach in women, and for diseases of the respiratory system and acute and chronic kidney failure in both sexes. Finally, analyses on risk of congenital malformations and adverse pregnancy outcomes showed a statistically significant increase of cases for urogenital anomalies and reduction of cases for low birth weight and preterm birth in the SGA and for congenital HD in the NGA (Minichilli et al, 2012).

An updated mortality analysis (Bustaffa et al, 2017) showed results similar respect to the previous survey (Minichilli et al, 2012). In the TGA the study found excesses for all causes, diseases of the respiratory system, in particular for pneumoconiosis and COPD among men and malignant neoplasms of ovary and other uterine adnexa and of the CNS and for diseases of the digestive system and, particularly chronic liver disease and cirrhosis among women. A decreased mortality was observed for malignant neoplasm of breast and ischemic HD among women (Bustaffa et al, 2017). In the NGA, results confirmed the excesses of mortality found in the TGA for diseases of respiratory system and pneumoconiosis, while a defect for all neoplasms, in particular for malignant neoplasm of trachea, bronchus, and lung was shown among men. Compared to the TGA, the increased mortality for malignant neoplasm of ovary and other uterine adnexa among women was confirmed and a new excess for cerebrovascular disease was observed (Bustaffa et al, 2017). In the SGA, in addition to previous results, excesses of deaths for all neoplasms, malignant neoplasm of stomach, liver, gallbladder and bile ducts, diseases of digestive system and chronic liver disease and cirrhosis among men and for acute respiratory infections and pneumonia in women were observed, whereas defects for malignant neoplasm of lymphatic and hematopoietic tissue and ischemic HD were detected among men and for diseases of the circulatory system in both sexes (Bustaffa et al, 2017).

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered.

NEW ZEALAND							
Study Design	**Study sample**	**Study Period**	**Exposure**	**Outcomes (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	n.d.	1981-1990	n.d.	Disease of the circulatory system (390-459)	SMR=0.94 (0.90-0.99) p=0.02	Age Calendar year Sex Ethnicity	Bates et al, 1997
				Acute rheumatic fever and chronic rheumatic heart disease (390-398)	SMR=1.51 (1.06-2.08) p=0.01		
				Hypertensive disease (401-405)	SMR=1.61 (1.24-2.05) p<0.001		
				Other heart disease (420-429)	SMR=0.70 (0.58-0.84) P<0.001		
				Diseases of the respiratory system (460-519)	SMR=1.18 (1.08-1.29) p<0.001		
				Pneumonia and influenza (480-487)	SMR=1.20 (1.04-1.38) p=0.008		
				Chronic obstructive respiratory disease and allied conditions (490-496)	SMR=1.20 (1.06-1.35) p=0.004		
				Disease of the circulatory system (390-459)	*Other (men)* SMR=0.91 (0.84-0.97) p=0.007	Age Calendar year	
				Diseases of the respiratory system (460-519)	*Maori (women)* SMR=1.61 (1.19-2.12) p=0.001		
Ecological	n.d.	1981-1990	n.d.	***Cancer*** Upper lobe, bronchus or lung (162.3)	SIR=0.65 (0.49-0.83) p=0.001	Age Calendar year Sex Ethnicity	Bates et al, 1998
				Bronchus and lung unspecified (162.9)	SIR=1.45 (1.13-1.84) p=0.002		
				Discharge Diseases of the nervous system and sense organs (320-389)	SIR=1.11 (1.07-1.15) p<0.001		
				Other disorders of the central nervous system (340-349)	SIR=1.35 (1.21-1.51) p<0.001		
				Infantile cerebral palsy (343)	SIR=1.42 (1.03-1.89) p=0.02		
				Migraine (346)	SIR=1.40 (1.12-1.72) p=0.002		
				Other conditions of brain (348)	SIR=2.50 (1.89-3.26) p<0.001		
				Disorders of the peripheral nervous system (350-359)	SIR=1.22 (1.11-1.33) p<0.001		
				Mononeuritis of upper limb and mononeuritis multiplex (354)	SIR=1.47 (1.29-1.67) p<0.001		
				Mononeuritis of lower limb (355)	SIR=2.06 (1.46-2.81) p<0.001		
				Disorders of the eye and adnexa (360-379)	SIR=1.12 (1.05-1.19) p<0.001		
				Cataract (366)	SIR=1.26 (1.14-1.38) p<0.001		
				Disorders of conjunctiva (372)	SIR=2.09 (1.66-2.59) p<0.001		
				Disorders of the orbit	SIR=1.69 (1.12-2.44) p=0.005		
				Hypertensive disease (401-405)	SIR=1.15 (1.00-1.32) p=0.05		
				Diseases of pulmonary circulation (415-417)	SIR=0.72 (0.54-0.93) p=0.01		
				Other heart disease (420-429)	SIR=1.06 (1.00-1.13) p=0.04		
				Cerebrovascular disease (430-438)	SIR=0.85 (0.79-0.91) p<0.001		
				Diseases of arteries, arterioles & capillaries (440-448)	SIR=1.17 (1.07-1.28) p=0.001		
				Diseases of veins & lymphatics & other circulatory diseases (451-459)	SIR=1.22 (1.15-1.29) p<0.001		
				Diseases of the respiratory system (460-519)	SIR=1.05 (1.02-1.07) p=0.001		
				Acute respiratory infections (460-466)	SIR=0.88 (0.83-0.93) p<0.001		
				Other diseases of the upper respiratory tract (470-478)	SIR=1.27 (1.20-1.33) p<0.001		
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	***Discharge*** **Diseases of the nervous system and sense organs (320-389)**	High: SIR=2.19 (1.99-2.41) Medium: SIR=1.31 (1.17-1.47) Low: SIR=1.23 (1.16-1.30) ptrend<0.001	Age Gender Ethnicity	Bates et al, 2002
				Other disorders of the central nervous system (340-349)	High: SIR=2.68 (2.01-3.50) Medium: SIR=1.67 (1.20-2.27) Low: SIR=1.38 (1.16-1.63) ptrend<0.001		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcomes (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	Disorders of the eye and adnexa (360-379)	High: SIR=2.27 (1.97-2.61) Medium: SIR=1.57 (1.30-1.89) Low: SIR=1.47 (1.33-1.63) ptrend<0.001	Age Gender Ethnicity	Bates et al, 2002
				Disorders of the ear and mastoid process (380-389)	High: SIR=2.00 (1.64-2.40) Medium: SIR=1.01 (0.83-1.21) Low: SIR=0.99 (0.91-1.08) ptrend<0.001		
				Disease of the circulatory system (390-459)	High: SIR=1.39 (1.29-1.50) Medium: SIR=0.95 (0.86-1.06) Low: SIR=1.08 (1.02-1.13) ptrend<0.001		
				Ischemic heart disease (410-414)	High: SIR=1.53 (1.35-1.73) Medium: SIR=0.89 (0.73-1.06) Low: SIR=1.20 (1.11-1.30) ptrend=0.02		
				Cerebrovascular disease (430-438)	High: SIR=1.14 (0.94-1.38) Medium: SIR=1.03 (0.80-1.31) Low: SIR=0.85 (0.74-0.97) ptrend=<0.01		
				Diseases of arteries, arterioles and capillaries (440-448)	High: SIR=1.66 (1.30-2.09) Medium: SIR=1.58 (1.17-2.08) Low: SIR=1.08 (0.90-1.29) ptrend<0.001		
				Diseases of the respiratory system (460-519)	High: SIR=1.65 (1.51-1.79) Medium: SIR=1.03 (0.94-1.14) Low: SIR=1.11 (1.06-1.16) ptrend<0.001		
				Acute respiratory infections (460-466)	High: SIR=1.77 (1.43-2.16) Medium: SIR=0.86 (0.69-1.05) Low: SIR=1.12 (1.02-1.22) ptrend=0.02		
				Other diseases of the upper respiratory tract (470-478)	High: SIR=1.98 (1.58-2.45) Medium: SIR=1.68 (1.39-2.01) Low: SIR=1.48 (1.34-1.63) ptrend=0.01		
				Pneumonia and influenza (480-487)	High: SIR=1.56 (1.31-1.85) Medium: SIR=1.02 (0.83-1.25) Low: SIR=1.09 (0.99-1.20) ptrend=0.002		
				Chronic obstructive respiratory disease and allied conditions (490-496)	High: SIR=1.57 (1.32-1.86) Medium: SIR=0.82 (0.66-1.02) Low: SIR=0.93 (0.84-1.03) ptrend<0.001		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcomes (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	Other diseases of the respiratory system (510-519)	High: SIR=1.51 (1.15-1.94) Medium: SIR=0.96 (0.68-1.34) Low: SIR=0.97 (0.82-1.14) ptrend=0.008	Age Gender Ethnicity	Bates et al, 2002
Spatial cluster analysis	12,215 visits	1991-2000	H_2S concentration High~1 ppm Medium~500 ppb Low~30-40 ppb	Diseases of the respiratory system (460-519)	1: RR=5.1; 2: RR=5.9	1: Age; Smoking; Deprivation 2: Ethnicity; Smoking; Deprivation	Durand and Wilson, 2006
				Other diseases of the upper respiratory system (470-478)	1: RR=8.7; 2: RR=8.2		
				Chronic obstructive pulmonary disease (COPD) (490-496)	1: RR=5.1; 2: RR=6.1		
				Asthma (493)	1: RR=7.6; 2: RR=10.5		
				Symptoms involving respiratory system and other chest symptoms	1: RR=7.9; 2: RR=11.8		
ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Cohort	74,806 individuals aged 5-65 GA 1,497 WRA 50,878 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.16 (1.00-1.34) CRA: HR=1.22 (1.05-1.42)	Age Gender Education Type of housing	Kristbjornsdottir and Rafnsson, 2012
				Pancreas (C25)	*Men+Women* WRA: HR=2.57 (1.30-5.07) CRA: HR=2.85 (1.39-5.86) *Men* WRA: HR=2.52 (1.01-6.28) CRA: HR=3.66 (1.37-9.82)		
				Bone (C40-C41)	*Women* WRA: HR=7.95 (1.70-37.23) CRA: HR=7.20 (1.30-39.96)		
				Breast (C50)	*Men+Women* WRA: HR=1.43 (1.00-2.05) CRA: HR=1.59 (1.10-2.31) *Women* WRA: HR=1.46 (1.02-2.09) CRA: HR=1.62 (1.12-2.36)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men+Women* CRA: HR=1.64 (1.00-2.66)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men+Women* WRA: HR=3.21 (1.77-5.82) CRA: HR=3.25 (1.73-6.07) Men WRA: HR=3.12 (1.43-6.78) CRA: HR=2.58 (1.16-5.78) *Women* WRA: HR=3.31 (1.32-8.34) CRA: HR=5.20 (1.87-14.45)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Cohort	74,806 individuals aged 5-65 GA 1,497 WRA 50,878 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	Basal cell carcinoma of the skin (Not included in all cancers)	*Men+Women* CRA: HR=1.61 (1.10-2.35) Men CRA: HR=1.78 (1.04-3.05)	Age Gender Education Type of housing	Kristbjornsdottir and Rafnsson, 2012
Census-based cohort study	73,309 individuals aged 5-64 HWSA 6,014 WRA 44,864 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.10 (1.01-1.20) CRA: HR=1.15 (1.05-1.25) *Men* WRA: HR=1.14 (1.01-1.27) CRA: HR=1.22 (1.08-1.37)	Age Gender Education Type of housing Smoking habits	Kristbjornsdottir and Rafnsson, 2013
				Oesophagus (C15)	*Men* CRA: HR=3.34 (1.35-8.26)		
				Breast (C50)	*Men+Women* WRA: HR=1.28 (1.04-1.59) CRA: HR=1.40 (1.12-1.75) *Women* WRA: HR=1.27 (1.02-1.58) CRA: HR=1.38 (1.11-1.73)		
				Prostate (C61)	*Men* WRA: HR=1.48 (1.21-1.82) CRA: HR=1.61 (1.29-2.00)		
				Kidney (C64-C66)	*Men and women* WRA: HR=1.51 (1.05-2.18) CRA: HR=1.64 (1.11-2.41) *Men* CRA: HR=1.76 (1.08-2.86)		
				Brain and central nervous system (C70-C72, C75.1 and C75.3)	*Men and women* WRA: HR=0.56 (0.32-0.98)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men and women* WRA: HR=1.51 (1.05-2.18) CRA: HR=1.64 (1.11-2.41) *Women* CRA: HR=1.66 (1.06-2.58)		
				Non-Hodgkin's lymphoma (C82-C85)	*Women* CRA: HR=2.50 (1.07-5.83)		
				Basal cell carcinoma of the skin (Not included in all cancers)	*Men and women* WRA: HR=1.24 (1.01-1.54) CRA: HR=1.46 (1.16-1.82) *Men* CRA: HR=1.46 (1.05-2.04) *Women* CRA: HR=1.43 (1.06-1.93)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	74806 individuals aged 5-64 GA 7511 WRA 44864 CRA 22431	1981-2009	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	Breast (C50)	*Women* RA: HR=1.49 (1.06-2.09)	Age Education Type of housing Smoking habits	Kristbjornsdottir and Rafnsson, 2015
				Prostate (C61)	*Men* RA: HR=1.88 (1.37-2.60)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men* RA: HR=2.31 (1.21-4.41)		
Population based cohort study	74806 individuals aged 5-64 GA 7511 WRA 44864 CRA 22431	1981-2013	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.10 (1.02-1.18) CRA: HR=1.21 (1.12-1.30) *Men+Women (5-years lat.)* WRA: HR=1.16 (1.03-1.30) CRA: HR=1.22 (1.08-1.37)	Age Gender Education Type of housing Smoking habits **HR with stratification into categories of cumulative years of residence**	Kristbjornsdottir et al, 2016
				Pancreas(C25)	*Men+Women* WRA: HR=1.53 (1.00-2.32) CRA: HR=1.93 (1.22-3.06) *Men+Women (5-years lat.)* WRA: HR=2.11 (1.03-4.34)		
				Breast (C50)	*Men+Women* WRA: HR=1.27 (1.07-1.52) CRA: HR=1.48 (1.23-1.80)		
				Prostate (C61)	WRA: HR=1.32 (1.11-1.57) CRA: HR=1.47 (1.22-1.77)		
				Kidney (C64-C66)	*Men+Women* CRA: HR=1.46 (1.03-2.05)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men+Women* WRA: HR=1.36 (1.08-1.72) CRA: HR=1.54 (1.21-1.97) *Men+Women (5-years lat.)* WRA: HR=1.61 (1.10-2.36) CRA: HR=1.70 (1.14-2.55)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men+Women* WRA: HR=1.90 (1.30-2.77) CRA: HR=2.08 (1.38-3.15) *Men+Women (5-years lat.)* WRA: HR=2.30 (1.27-4.14) CRA: HR=3.02 (1.52-6.00)		
				Basal cell carcinoma of the skin (C44)	WRA: HR=1.28 (1.08-1.52) CRA: HR=1.62 (1.35-1.94) *Men+Women (5-years lat.)* CRA: HR=1.48 (1.12-1.96)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcome (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	Average resident population in Geothermal Area: 43,440 subjects (16,902 in NGA and 26,358 in SGA). 21,031 Men 22,409 Women	2000-2006	--	***Mortality*** All causes (0-999)	*TGA* - M: SMR=108 (103-112) *SGA* - M: SMR=115 (109-121)	Deprivation index	Minichilli et al, 2012
				Infectious and parasitic diseases (001-139)	*TGA* - M: SMR=245 (159-362) *SGA* - M: SMR=250 (125-447)		
				Neoplasms (140-239)	*NGA* - M: SMR=87 (76-98) *SGA* - M: SMR=121 (110-131)		
				Malignant neoplasm of liver and intrahepatic bile ducts (155)	*TGA* - M: SMR=138 (104-179) *SGA* - M: SMR=171 (122-234)		
				Malignant neoplasm of trachea, bronchus, and lung (162)	*SGA* - M: SMR=121 (101-145)		
				Malignant neoplasm of ovary and other uterine adnexa (183)	*NGA* - W: SMR=172 (100-275)		
				Disorders of the nervous system and sense organs (320-389)	*TGA* - M: SMR=130 (101-163)		
				Ischemic heart disease (410-414)	*TGA* - W: SMR=85 (74-97)		
				Cerebrovascular disease (430-438)	*NGA* - W: SMR=122 (104-142)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SMR=129 (112-147) *SGA* - M: SMR=132 (110-157)		
				Acute respiratory infections (460-466)	*SGA* - W: SMR=142 (102-193)		
				Pneumoconiosis (500-505)	*TGA* - M: SMR=372 (277-489) *NGA* - M: SMR=351 (214-542) *SGA* - M: SMR=388 (263-550)		
				Diseases of the digestive system (520-579)	*SGA* - W: SMR=130 (102-164)		
				Chronic liver disease and cirrhosis (571)	*NGA* - W: SMR=143 (100-199)		
				Hospitalization All causes (0-999)	*NGA* - W: SHR=106 (100-111)		
				Malignant neoplasm of stomach (151)	*TGA* - W: SHR=153 (110-206) *SGA* - W: SHR=161 (108-231)		
				Malignant neoplasm of liver and intrahepatic bile ducts (155)	*SGA* - M: SHR 160 (101-240)		
				Malignant neoplasm of lymphatic and hematopoietic tissue (200-208)	*TGA* - W: SHR=139 (102-186)		
				Leukemia (204-208)	*TGA* - W: SHR=262 (131-469) *NGA* - W: SHR=181 (109-283)		
				Parkinson's disease (332)	*SGA* - M: SHR=227 (109-418)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SHR=111 (103-120) *SGA* - M: SHR=116 (105-128) W: SHR=122 (110-136)		
				Diseases of the digestive system (520-579)	*NGA* - M: SHR=112 (101-124) W: SHR=112 (100-125)		
				Acute and chronic renal failure (584-585)	*SGA* - M: SHR=150 (115-193) W: SHR=153 (114-200)		
				Congenital heart disease	*NGA*: O/E: 43 (14-99)		
				Urogenital anomalies	*SGA*: O/E: 210 (109-367)		
				Low-birth weight	*SGA*: O/E: 72 (53-95)		
				Gestational age < 37 weeks	O/E: 75 (57-98)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcome (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	Average resident population in Geothermal Area: 40,461 subjects (16,630 in NGA and 23,831 in SGA). 19,678 Men 20,784 Women	203-2012	--	All causes (0-999)	*TGA* – M: SMR=103 (100-107) *SGA* - M: SMR=109 (104-114)	Deprivation index	Bustaffa et al, 2017
				Neoplasms (140-239)	*NGA* - M: SMR=86 (77-95) *SGA* - M: SMR=116 (107-125)		
				Malignant neoplasm of stomach (151)	*SGA* - M: SMR=146 (114-185)		
				Malignant neoplasm of liver, gallbladder and bile ducts (155,156)	*SGA* - M: SMR=153 (116-199)		
				Malignant neoplasm of trachea, bronchus, and lung (162)	*NGA* - M: SMR=72 (56-91)		
				Malignant neoplasm of breast (174-175)	*TGA* - W: SMR=77 (61-97)		
				Malignant neoplasm of ovary and other uterine adnexa (183)	*TGA* - *W*: SMR=138 (102-183) *NGA* - W: SMR=164 (103-248)		
				Malignant neoplasm of lymphatic and hematopoietic tissue (200-208)	*SGA* - M: SMR=69 (47-97)		
				Malignant neoplasm of the central nervous system (191-192, 225, 239.6)	*TGA* – W: SMR=148 (104-203) *SGA* - W: SMR=184 (123-264)		
				Diseases of the circulatory system (390-459)	*SGA* - M: SMR=91 (84-99) W: SMR=93 (87-99)		
				Ischemic heart disease (410-414)	*TGA* - W: SMR=81 (73-91) *SGA* - M: SMR=79 (68-91) W: SMR=76 (65-88)		
				Cerebrovascular disease (430-438)	*NGA* - W: SMR=115 (101-132)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SMR=134 (120-149) *NGA* - M: SMR=132 (111-155) *SGA* - M: SMR=135 (117-155)		
				Acute respiratory infections (460-466)	*SGA* - W: SMR=142 (107-186)		
				Pneumonia (487)	*SGA* - W: SMR=137 (100-184)		
				Chronic obstructive pulmonary disease (491-492, 494-496)	*TGA* - M: SMR=119 (101-139)		
				Pneumoconiosis (500-505)	*TGA* - M: SMR=325 (258-406) *NGA* - M: SMR=364 (256-502) *SGA* - M: SMR=298 (215-402)		
				Diseases of the digestive system (520-579)	*TGA* - W: SMR=134 (114-155) *SGA* - M: SMR=127 (101-157) W: SMR=147 (121-176)		

Notes – n.d.: not defined; ICD: International Classification of Disease; 95%CI: 95% Confidence Interval; SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; H_2S: Hydrogen Sulfide; ppm: part per million; ppb: part per billion; RR: Relative Risk; GA: Geothermal Area; WRA: Warm Reference Area; CRA: Cold Reference Area; HR: Hazard Ratio; HWSA: Hot Water Supply Area; RA: Reference Area; TGA: Total Geothermal Area; NGA: Northern Geothermal Area; SGA: Southern Geothermal Area; M: men; W: women; SHR: Standardize Hospitalization Ratio; O/E: Observed/Expected.

3.2 Studies based on proxy-individual level exposure metrics

3.2.1 New Zealand

All the five studies of this paragraph (Bates et al, 2017, 2015, 2013; Reed et al, 2014; Pope et al, 2017) used the same method for the H_2S exposure estimation in and around Rotorua. Particularly, H_2S concentrations were calculated at each subject's residential, workplace and school locations using measurements from three monitoring networks (summer and winter 2010 and winter 2011) deployed across Rotorua for two-week periods (Bates et al, 2013). These data were used to calculate weighted average H_2S concentrations at each location while two types of H_2s exposure metric were applied: the mean time-weighted average exposure (based on hours at work or school assuming the remainder was spent at home) and the maximum average exposure (derived selecting the higher of the average home, work or school exposure). Exposure metrics were created for both time of participation ("current exposure") and for the last 30 years ("long-term exposure").

The investigation on the association between H_2S exposure and asthma in adults revealed no increased risk, nevertheless indications of exposure-related reduced risks for diagnosed asthma and asthma symptoms, particularly wheezing during the last 12 months, emerged (Bates et al, 2013). Reed et al. (2014) investigated cognitive effects of ambient H_2S concentrations. A wide range of cognitive functions were evaluated such as attention, memory, psychomotor speed, fine motor function and mood. The authors observed that notwithstanding higher levels of H_2S were sometimes associated with slightly better performance, namely subjects with the higher exposure had faster average reaction times compared to the lowest exposure group, the overall results provide no evidence that chronic H_2S exposure was associated with impairment of cognitive function (Reed et al, 2014). A more recent survey investigated associations of H_2S exposure with lung function, COPD and asthma (Bates et al, 2015). For all participants combined and for all subgroups, no evidence of an adverse association between the ambient H_2S levels and any of the spirometric parameters examined or COPD were observed (Bates et al, 2015). On the other hand, considering the relationship between H_2S and older participants separately, dichotomized by smoking, asthma and COPD statuses, some suggestions that long-term H_2S exposure might mitigate lung damage in smokers were detected, although the association was not clearly evident in those with COPD (Bates et al, 2015). Considering the previous findings for cataract and an exposure-response relationship for disorders of the eye and adnexa (Bates et al, 1998), Bates et al. (2017) investigated the relationship of long-term, ambient exposure to H_2S increased levels of lenticular changes and cataract, without finding any evidence of association. In a subsequent study to that of Bates et al. (2002), who reported positive association between the estimated H_2S exposure and hospital discharge diagnoses for disorders of the peripheral nervous system, Pope et al. (2017) provide no evidence of correlation between any of the indicators of peripheral neuropathy and exposure to ambient air H_2S over a period of 30 years.

3.2.2. Iceland

In small populations, like those of Iceland, the use of anti-asthma drugs (medication to relieve the symptoms of obstructive respiratory diseases), has been suggested as a more sensitive marker for respiratory morbidity than hospital emergency room visits and hospital admissions (Menichini and Mudu, 2010). Furthermore, a significant correlation was reported between individual emergency room visits for asthma and subsequent prescription fills for instant asthma symptom-relieving drugs (Naureckas et al, 2005). Considering these factors, Carlsen et al. (2012) investigated the associations between daily ambient levels of H_2S, PM_{10}, NO_2 and O_3, and the use of anti-asthma drugs for obstructive pulmonary diseases in adults in Iceland's capital area. The study revealed that small increases in H_2S levels over a three-day period were associated with a modest but significant higher number of individuals who were dispensed anti-asthma drugs 3 to 5 days later (Carlsen et al, 2012). The effect associated with PM_{10} was generally smaller but more significant for the three-day average of 1-h peak pollution than for the three-day average of the 24-h mean pollution. This was reversed for H_2S, as the association was only significant for the three-day moving average of the 24-h mean and not for the 1-h peak pollution (Carlsen et al, 2012).

The setting in the Reykjavik capital area with access to nation-wide both death registry and hospital admissions and population registries, and the continuous monitoring of ambient air pollutants offers an opportunity to evaluate health indicators associated to short-term increases of traffic-related pollutants and, in particular, of geothermal source-specific H_2S with mortality (Finnbjornsdottir et al, 2015) and of low-level H_2S exposed inhabitants in the Reykjavik capital area (Finnbjornsdottir et al, 2016). In fact, Finnbjornsdottir et al. (2015) investigated the association between daily mortality and short-term increases in air pollutants, both traffic related and the geothermal source-specific H_2S. A lag time of up to 4 days (five lags: 0–4) was introduced separately to the analyses. Lag definitions are as follows: lag 0: air pollution exposure on the same day as death occurred, lag 1–4: air pollution exposure 1 day before (lag 1) and up to 4 days before (lag 4) the death occurred. Results shown as percentage increases in risk of death showed a statistically significant decreased risk at lag 3 in the unstratified model for H_2S. A statistically significant increased risk at lag 1 and 2 was observed in summer while in winter there was a statistically significant decreased risk at lag 3, corresponding to the increase during the summer months. An increased risk at lag 0 among men was found. For individuals who were 80 years of age and older, there was a statistically significant elevation of risk at lag 0 and lag 1, and among individuals younger than 80 years of age there was a statistically significant decrease at lag 2. The results indicated the association between higher concentrations of H_2S and daily all natural cause deaths in the Reykjavik area. These associations were strong and statistically significant during summer months among men, and among elderly when adjusted for traffic-related pollutants and meteorological variables (Finnbjornsdottir et al, 2015). Short-term associations between modelled ambient low-level intermittent H_2S concentrations and daily hospital admissions and emergency department visits with HD, respiratory disease and stroke as primary diagnoses among individuals living in the Reykjavik capital area were assessed in the study of Finnbjornsdottir et al. (2016). Considering the un-stratified models for increases in emergency hospital visits with HD as primary diagnosis, trend analyses between different levels of exposure (from 50 to 95 percentiles) the dose-response relationship was positive at lag 0 and 2 and negative at lag 4. Stratifying by gender, the same results were observed among women. The age stratification showed positive dose-response relationship at lags 0, 2 and 3 among those 73 years old and older. The relative risks for the association between H_2S at different percentiles and emergency hospital visits with respiratory diseases as primary diagnosis showed some significant trends through different levels of exposure at lag 0 and 3 in the un-stratified analysis, in men at lags 0 and 2 and at lags 0 and 3 in the older strata, indicating a negative dose-response association. Considering stroke as primary diagnosis the same analyses showed a statistically significant positive association at lag 0 in the un-stratified, men and the older stratum and a statistically significant negative association at lag 1 in the same stratum, indicating dose-response manner of associations (Finnbjornsdottir et al, 2016).

3.2.3. Italy

The association between chronic low-level exposure to H_2S and health outcomes, using a residential cohort study, was explored through a H_2S dispersion model based on georeferenced residence address of the cohort members (Nuvolone et al, 2019). Negative associations were observed in the general population and among women between level of exposure to H_2S, computed both as a categorical and continuous variable, and mortality for natural causes and malignant neoplasms. A decreased risk of mortality was also found in the most exposed subjects for ischemic HD and acute myocardial infarction in the overall sample and in men, and for cerebrovascular diseases in the general population and stratifying by sex, and for diseases of circulatory system among men in the moderately exposed subjects. Conversely, mortality increased in the general population and in women for diseases of the respiratory system and, exclusively among women, for pneumonia in the continuous model. Hospitalization analysis confirmed decreased risks for all neoplasms per 7 $\mu g/m^3$ increase of H_2S, except for malignant neoplasm of ovary and other uterine adnexa. An excess of risk per 7 $\mu g/m^3$ increase of H_2S was also observed for disorders of the nervous system and sense organs in the general population, and for disorders of the peripheral nervous system, considering also each sex separately. As for diseases of circulatory system, a slight excess of hospital admission was detected in the general population, and a more pronounced risk for heart failure and diseases of veins and lymphatics was found in both sexes considering categorical metrics. In contrast, cerebrovascular diseases showed decreased risks associated with H_2S exposure considering the total sample in the continuous as well as in the categorical model. Finally, the results for respiratory diseases were consistent with mortality analysis, with the strongest association observed for COPD among high-level exposed men and pneumonia among the most exposed women (Nuvolone et al, 2019).

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered.

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Cross-sectional	1637 subjects aged 18-65	2008-2010	Wheeze or whistling	**Prevalence ratio by quartile (Q) of maximum H_2S exposure concentrations** Q2 Vs Q1 0.98 (0.81-1.19) Q3 Vs Q1 0.87 (0.71-1.08) Q4 Vs Q1 0.80 (0.65-0.99) ptrend=0.02	Estimated from data collected by summer and winter H_2S monitoring networks. Median H_2S concentration 0-64 ppb (averaged between winter and summer): for residences 20.3 ppb (mean 20.8 ppb) and for workplaces 26.4 ppb (median 27.7 ppb). Calculation of four metrics for H_2S exposure, representing current and long term exposure and TWM exposure and MWH. For TWM exposure: Q1 (0-10 ppb) as reference Q2 (11-20 ppb) Q3 (21-30 ppb) Q4 (31-64 ppb) For MWH exposure: Q1 (0-10 ppb) as reference Q2 (11-20 ppb) Q3 (30-44 ppb) Q4 (45-64 ppb)	Sex Smoking habits Age Ethnicity Education level Employment status	Bates et al, 2013
Cross-sectional	1637 subjects aged 18-65 having lived in Rotorua for at least the last 3 years	2008-2010	Attention, psychomotor speed, memory, fine motor skills, mood	**No association between H_2S exposure and cognitive function.** **Slightly better performance of simple reaction time and digit correct symbol for higher levels of H_2S (Q4) both for current (a) and long term (b) exposure and both for time-weighted mean (TWM) exposure and maximum exposure at work or home (MWH).** _Simple reaction time (a)_ TWM Q4 Vs Q1 -2.3 (-6.3-1.6) MWH Q4 Vs Q1 -4.1 (-8.0-(-0.1)) _Digit symbol correct (a)_ TWM Q4 Vs Q1 1.1 (-0.4-2.5) MWH Q4 Vs Q1 1.2 (-0.2-2.7) _Simple reaction time (b)_ TWM Q4 Vs Q1 -1.8 (-5.9-2.2) MWH Q4 Vs Q1 -3.0 (-7.1-1.1) _Digit symbol correct (b)_ TWM Q4 Vs Q1 0.7 (-0.8-2.2) MWH Q4 Vs Q1 0.6 (-0.9-2.1)		Age Sex Ethnicity Education Income Alcohol consumption, NART Examiner	Reed et al, 2014
Cross-sectional	1,204 subjects aged 18-65 414 men 790 women	2008-2010	Asthma and Chronic Obstructive Pulmonary Disease (COPD)	**No evidence (for all participants combined and all subgroups) of an adverse association between the ambient H_2S levels in Rotorua and any of the spirometric parameters examined or COPD**		Sex Smoking habits Age Ethnicity Education level Employment status Income	Bates et al, 2015
Cross-sectional	1,637 subjects aged 18-65	---	4 outcome categories to assess lens opacity (based on LOCS score) Nuclear Opacity Nuclear Color Cortical Opacity PSC opacity	**No evidence of an association between H_2S exposure and LOCS score in any of the 4 outcome categories**		Age Smoking habits	Bates et al, 2017

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Ecological	1,635 subjects aged 18-65	2008-2010	Neuropathy evaluated through: Ankle Reflex Test Filsment Test Tuning Fork Bio-Thesiometer NCIS (Neuropathy Composite Index Score)	**No evidence of an association of any of the indicators of peripheral neuropathy with exposure to ambient H_2S over a period of 30 years.**	An average time-weighted H_2S exposure over the last 30 years was calculated for each participant. Concentrations surfaces were created using kriking. Range 0-58 ppb (median 11 ppb, average 13 ppb) 4 exposure categories defined Q1 (0-5.6 ppb); Q2 (5.6-10.6 ppb) Q3 (10.6-18.4 ppb): Q4 (18.4-57.9 ppb)	Age Ethnicity Education level Income	Pope et al, 2017
Time series	--	2006-2009	Excess risk (%) of increased dispensing of anti-asthma drugs (alla drugs and adrenergic drugs) Results given per 10 µg/m^3 pollutant increase	**H_2S** *24-h mean pollution (all drugs)* Lag (3-5) ER 2% (0.4-3.6) **PM_{10}** *24-h mean pollution (all drugs)* Lag (3-5) ER 0.9% (0.1-1.8) Lag (6-8) ER -1.3% (-2.1-(-0.5)) *24-h mean pollution (adrenergic drugs)* Lag (3-5) ER 1.3% (0.4-2.2) Lag (6-8) ER -1.7% (-2.6-(-0.8)) *1-h peak pollution (all drugs)* Lag (3-5) ER 0.3% (0.2-0.4) Lag (6-8) ER 0.1% (0.0-0.2) Lag (9-11) ER 0.1% (0.0-0.2) Lag (12-14) ER 0.1% (0.0-0.2) *1-h peak pollution (adrenergic drugs)* Lag (3-5) ER 0.3% (0.2-0.5) Lag (6-8) ER 0.1% (0.0-0.3) Lag (9-11) ER 0.1% (0.0-0.2)	Daily (midnight to midnight) 1-h peak pollution and daily 24-h mean concentrations. For each day authors calculated the three-day moving average from the daily mean and peak values of the same day, the day before and two day before (lag 0-2), 3 to 5 day before (lag 3-5), 6 to 8 day before (lag 6-8), 9-11 day before (lag 9-11) and 12.14 day before (lag 12-14)	Temperature Relative humidity Total pollen count Influenza epidemics Day-of week and holiday binary variables Time trend Season trend	Carlsen et al, 2012
Cross-sectional	181,558 subjects >18 year	2003-2009	Percentage increases in risk of death (IR%) for all natural cause (ICD-10 code A00-R99) following an interquartile range increase in pollutants. Analyses perfomred stratifying on season (winter/summer), gender and age (<80 years and ≥80)	**H_2S** *Un-stratified model* lag3 IR%=-1.54 (-3.00-(-0.05)) *Summer* lag1 IR%=5.05 (0.61-9.68) *Summer* lag2 IR%=5.09 (0.44-9.97) *Winter* lag3 IR%=-1.99 (-3.55-(-0.41)) *Males* lag0 IR%=2.26 (0.23-4.33) *≥80 years* lag0 IR%=1.94 (0.12-1.04) *≥80 years* lag1 IR%=1.99 (0.21-1.04) *<80 years* lag2 IR%=-2.87 (-5.38-(0.30)) **PM_{10}** *<80 years* lag0 IR%=2.81 (0.00-5.70)	A lag time of up to 4 days (five lags: 0–4) was introduced separately to the analyses. Lag definitions are as follows: lag 0: air pollution exposure on the same day as death occurred, lag 1–4: air pollution exposure 1 day before (lag 1) and up to 4 days before (lag 4) the death occurred. Pollutants: NO_2, PM_{10}, SO_2, H_2S, O_3	Each pollutant Temperature Relative humidity	Finnbjornsdottir et al, 2015

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Population-based cohort	13,383 patients (≥18 years old) with a total of 32961 emergency hospital visits	2007-2014	**Heart diseases:** Ischemic heart diseases (I20-I27) Cardiac arrest (I46) Cardiac arrhythmias (I48) Heart failure (I50)	**Unstratified model**[a] Lag0 p-trend=0.0038 (+) Lag2 p-trend=0.0027 (+) Lag4 p-trend=0.0483 (-) **Gender stratification**[b] <u>*Females*</u> Lag0 p-trend=0.0000 (+) Lag2 p-trend=0.0004 (+) Lag4 p-trend=0.0010 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0000 (+) Lag2 p-trend=0.0000 (+) Lag3 p-trend=0.0000 (+)	Ambient air concentrations for NO_2, O_3, PM_{10}, SO_2 and H_2S in μg/m^3 Meteorological data: temperature, relative humidity, wind speed and wind direction. H_2s concentrations divided in five 10° sections (A-E) and the average 24-hour H_2S concentration in each section was calculated. Different exposure levels of H_2s were estimated by different percentiles: 50% 2.46 μg/m^3 60% 3.16 μg/m^3 70% 4.14 μg/m^3 80% 5.74 μg/m^3 85% 7.00 μg/m^3 90% 8.80 μg/m^3 95% 11.68 μg/m^3. Distance from main roads (>10.000 cars per day) in the Reykjavik capital area was calculated for each individual's residential street and divided into categories of traffic exposure zones and used as a surrogate for traffic related exposure. To estimate H_2S exposure in different sections of the Reykjavik capital area, a simple model was applied covering a 50° section from Hellisheidi power plant to the west, which includes the Reykjavik capital area.	[a]Gender, age group, season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature [b]Age group, season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature [c]Season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature	Finnbjornsdottir et al, 2016
			Respiratory diseases Acute lower respiratory infections (J20-J22) Chronic lower respiratory infections (J40-J46) Respiratory failure (J96)	**Un-stratified model**[a] Lag0 p-trend=0.0340 (-) **Gender stratification**[b] <u>*Males*</u> Lag0 p-trend=0.0003 (-) Lag2 p-trend=0.000 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0000 (-) Lag3 p-trend=0.0013 (-)			
			Stroke: Cerebrovascular diseases (I61-I69) other than subarachnoid haemorrhage (I60) and transient cerebral ischaemic attacks and related syndromes (G45) and vascular shyndromes of brain in cerebrovascular diseases (G46)	**Un-stratified model**[a] Lag0 p-trend=0.0038 (+) Lag1 p-trend=0.0086 (-) **Gender stratification**[b] <u>*Males*</u> Lag0 p-trend=0.0104 (+) Lag1 p-trend=0.0002 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0136 (+) Lag1 p-trend=0.0042 (-) *p-trend across the percentiles of H_2S concentrations;* *(+) positive dose-response association* *(-) negative dose-response association*			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	***Mortality*** Non-accidental mortality (0-999)	<u>*Men+women*</u> HR II *vs* I=0.82 (0.77-0.87); p<0.0001 HR III *vs* I=0.87 (0.79-0.96); p=0.006 HRlinear=0.94 (0.91-0.97); p<0.001 <u>*Women*</u> HR II *vs* I=0.76 (0.70–0.82); p<0.001 HR III *vs* I= 0.82 (0.71–0.94); p<0.001	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 μg/m^3 not-exposed; Group II: 5–20 μg/m^3 – low exposure; Group III: >20 μg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 μg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			All malignant neoplasms (140-239)	<u>*Men+women*</u> HR II *vs* I=0.83 (0.75-0.92); p<0.001 HR III *vs* I=0.79 (0.65-0.95); p=0.015 HRlinear=0.92 (0.87-0.97); p=0.009 <u>*Women*</u> HR II *vs* I=0.75 (0.63–0.89); p=0.001 HR III *vs* I=0.63 (0.45–0.83); p=0.003			
			Diseases of the circulatory system (390-419)	<u>*Men*</u> HR II *vs* I=0.84 (0.72–0.98); p=0.038			
			Ischemic heart disease (410-414)	<u>*Men+women*</u> HR III *vs* I=0.60 (0.41-0.88); p=0.011 HRlinear=0.85 (0.76-0.95); p=0.004 <u>*Men*</u> HR III *vs* I=0.49 (0.28–0.87); p=0.016			
			Acute myocardial infarction (410)	<u>*Men+women*</u> HR III *vs* I=0.45 (0.25-0.81); p=0.007 HRlinear 0.75 (0.63-0.89); p=0.001 <u>*Men*</u> HR III *vs* I=0.36 (0.15–0.86); p=0.018			
			Cerebrovascular diseases (430-438)	<u>*Men+women*</u> HR II *vs* I=0.74 (0.61-0.90); p=0.002 <u>*Men*</u> HR III *vs* I= 0.70 (0.51–0.96); p=0.025 <u>*Women*</u> HR II *vs* I=0.76 (0.59–0.97); p=0.036			
			Diseases of the respiratory system (460-519)	<u>*Men+women*</u> HRlinear 1.12 (1.00-1.25); p=0.040 <u>*Women*</u> HR II *vs* I=1.47 (1.00–2.15); p=0.046			
			Pneumonia (487)	<u>*Men+women*</u> HRlinear 1.27 (1.02-1.58); p=0.031			
			Hospitalization All malignant neoplasms (140-239)	<u>*Men+women*</u> HR III *vs* I=0.86 (0.75-0.98); p=0.034 HRlinear 0.95 (0.91-0.99); p=0.049			
			Malignant neoplasm of ovary and other uterine adnexa (183)	<u>*Men+women*</u> HRlinear 1.40 (1.07-1.84); p=0.014 <u>*Women*</u> HR II *vs* I=2.64 (1.40–4.98); p=0.003 HR III *vs* I=2.50 (1.00–6.25); p=0.049			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	Diseases of the nervous system and sense organs (320-389)	<u>*Men+women*</u> HR II *vs* I=1.13 (1.03-1.24); p=0.006 HRlinear 1.06 (1.01-1.11); p=0.003	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 μg/m^3 not-exposed; Group II: 5–20 μg/m^3 – low exposure; Group III: >20 μg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 μg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			Disorders of the peripheral nervous system (350-359)	<u>*Men+women*</u> HR II *vs* I=1.77 (1.42-2.21); p<0.001 HR III *vs* I=1.61 (1.13-2.30); p=0.008 HRlinear 1.22 (1.10-1.36); p<0.001 <u>*Men*</u> HR III *vs* I=1.66 (1.15–2.40); p=0.007 <u>*Women*</u> HR II *vs* I=1.83 (1.38–2.43); p<0.001 HR III *vs* I=1.81 (1.18–2.78); p=0.006			
			Diseases of the circulatory system (390-459)	<u>*Men+women*</u> HRlinear 1.04 (1.01-1.07); p=0.006			
			Heart failure (428)	<u>*Men+women*</u> HR III *vs* I=1.54 (1.26-1.94); p<0.001 HRlinear 1.14 (1.07-1.22); p<0.001 <u>*Men*</u> HR III *vs* I=1.42 (1.04–1.95); p=0.026 <u>*Women*</u> HR III *vs* I=1.65 (1.23–2.21); p=0.001			
			Cerebrovascular diseases (430-438)	<u>*Men+women*</u> HRlinear 0.93 (0.88-0.98); p=0.017 HR II *vs* I=0.87(0.79–0.96); p=0.015 HR III *vs* I=0.78 (0.65–0.94); p=0.008			
			Diseases of veins and lymphatics, and other diseases of circulatory system (451-459)	<u>*Men+women*</u> HR II *vs* I=1.46 (1.28-1.66); p<0.001 HRlinear 1.15 (1.08-1.22); p<0.001 <u>*Men*</u> HR II *vs* I=1.54 (1.28–1.86); p<0.001 <u>*Women*</u> HR II *vs* I=1.40 (1.17–1.68); p<0.001 HR III *vs* I=1.35 (1.02–1.80); p=0.035			
			Pneumonia (487)	<u>*Men+women*</u> HR II *vs* I=1.36 (1.18-1.57); p<0.0001 <u>*Men*</u> HR II *vs* I=1.35 (1.11–1.64); p=0.002<u>*Women*</u> HR II *vs* I=1.37 (1.10–1.71); p=0.005 HR III *vs* I=1.64 (1.18–2.28); p=0.003			
			Chronic obstructive pulmonary disease, and allied conditions (490-496)	<u>*Men+women*</u> HRlinear 1.14 (1.06-1.23); p<0.001 HR II *vs* I=1.30 (1.08-1.57); p=0.006 HR III *vs* I=1.98 (1.49-2.63); p<0.0001			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	Chronic obstructive pulmonary disease, and allied conditions (490-496)	*Men* HR III *vs* I=2.09 (1.45–3.02; p<0.0001 *Women* HR II *vs* I=1.44 (1.06–1.95); p=0.015 HR III *vs* I=1.84 (1.18–2.86); p=0.007	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 µg/m^3 not-exposed; Group II: 5–20 µg/m^3 – low exposure; Group III: >20 µg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 µg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			Other diseases of the respiratory system (510-519)	*Men+women* HR II *vs* I=0.57 (0.49-0.66); p<0.0001 HR III *vs* I=0.59 (0.47-0.77); p<0.0001 HRlinear 0.77 (0.74-0.84); p<0.001 *Men* HR II *vs* I= 0.56 (0.47–0.66); p<0.0001 HR III *vs* I= 0.62 (0.47–0.82); p=0.003 *Women* HR II *vs* I= 0.55 (0.44–0.69); p<0.0001 HR III *vs* I=0.60 (0.41–0.88); p=0.009			

Notes – vs: versus; ppb: part per billion; NO_2: nitrogen dioxide; O_3: Ozone; PM_{10}: particulate matter with diameter <10 µm; SO_2: sulfur dioxide; H_2S: hydrogen sulfide; HR: Hazard Ratio.

4. Discussion

For different reasons the context of industrial geothermal development does not facilitate the connection between environment and health. The papers overviewed in our analysis offer a very good example of this difficulty. The purpose of this review was to describe the health status of communities living in geothermal areas or near geothermal plants producing electric energy or circulating fluids for domestic use, which experience an exposure to H_2S, in most cases with the absence of potentially confounding co-pollutants. In fact, while the effects on human health caused by the exposure to high concentrations of H_2S (>250 ppm) are well characterized (sudden death, loss of consciousness and pulmonary edema) (ATSDR, 2016, American Conference of Governmental Industrial Hygienists (ACGIH, 2010), on the other hand evident human health hazards associated with chronic exposure to low concentration of H_2S need to be still elucidated. The studies overviewed in our analysis were conducted in three geographical areas and should be considered also in view of the different exposure. In Taupō, New Zealand, the population is continuously exposed to the strong (one or two orders of magnitude higher than in the other cases) natural degassing from the soils, and the effects to industrial facilities is negligible. In Iceland there are two different cases: a) the surveys related to Reykjavik, where people are variably exposed, depending on the location and the atmospheric plume dispersion, to continuous emissions form the two geothermal power plants and b) the population-based studies in the island excluding the capital area, referred to a daily exposure to geothermal fluids domestic purposes. In Italy, as in the Reykjavik case, the exposure is variable although the emitters are essentially continuous and represented by geothermal electricity plants.

As previously specified, we classified the articles selected in studies based on health indicators and studies that also consider proxy-level exposure measures at the individual level. It is worth of notes that most studies have an ecological design. Overall, the major limitations of this kind of studies are the use of the residence at municipal level as a proxy of exposure to both environmental and socioeconomic factors as well as of aggregated data of health outcomes, thus they do not provide evidence sustaining a judgment on the cause-effect relationship (Elliott et al, 2000). Despite these limits, it should be noted that information from a population-based ecological study is generally used in public health as a generator of hypotheses to be further evaluated in investigations with etiological design. Moreover, the results obtained from ecological studies may complete measures about the strength of the association between the environmental exposure and risk of health outcomes at individual level, providing a more accurate space-time definition of the phenomenon (Schwartz, 1994; Pearce, 2000).

In Rotorua, studies conducted at the end of the 90's, based on health indicators, did not find substantial indications of excess of mortality (Bates et al, 1997) while hospital discharge data suggested increased risks for disorders of the nervous system and the eye (Bates et al, 1998). Following the first classifications of the exposure (installation of the first samplers), an increased incidence for neurological effects and diseases of circulatory and respiratory systems emerged (Bates et al, 2002; Durand and Wilson, 2006). Overall, studies based on proxy-level exposure metrics at the individual level conducted in New Zealand did not report any association between chronic exposure to H_2S at ambient levels found in and around Rotorua, asthma or asthma symptoms (Bates et al, 2013) and impairment of pulmonary function and COPD (Bates et al, 2015), impairment cognitive function or mood (authors surprisingly observed better performance for higher exposure for some neurophysiological measures) (Reed et al, 2014), peripheral neuropathy (Pope et al, 2017) and cataract (Bates et al, 2017). The previous observed associations between H_2S exposure and both cataract and peripheral neuropathy in the Rotorua populations (Bates et al, 2002) seems likely to be attributable to the limitations of the ecological study design and the potential presence of unknown confounding factors or, alternatively, systematic biases in data records did not allow authors to link these findings to geothermal emissions. Nonetheless, there are some signals to be pointed out. The reduced risk for asthma and respiratory symptoms detected among the subjects exposed to higher H_2S (Bates et al, 2013) and the suggestion that long-term H_2S exposure might mitigate lung damage in smokers, although the association was not clearly evident in subjects with COPD (Bates et al, 2015), are consistent with literature. Indeed, some evidence supports the hypothesis of beneficial signaling functions of H_2S for humans as endogenously produced H_2S has anti-inflammatory and cytoprotective roles (e.g., induction of smooth muscle relaxation) (Olson and Donald, 2009; Whiteman et al, 2011). These findings have led to suggestions of possible therapeutic benefits of H_2S (Faller et al, 2010; King and Lefer, 2011). The key limitations of the New Zealand studies are the ecological design and the lowest response rate (for Bates et al. 2015, 2013 and Reed et al, 2014) even if these issues did not affect results.

In Iceland, studies based on health indicators have been conducted since 2012 and showed higher risks for several cancers, particularly for cancer of pancreas, breast, prostate, kidney, lymphoid and haematopoietic tissue, NHL and BCC of the skin for longer exposure to geothermal waters for domestic use (Finnbjornsdottir et al, 2015; Kristbjornsdottir et al, 2016; Kristbjornsdottir and Rafnsson, 2013, 2012). In Reykjavick area studies including exposure assessment found associations between H_2S exposure and short-term increase in the need for anti-asthmatic drugs in the adult population also exposed to PM_{10}, (Carlsen et al, 2012), an increased mortality (Finnbjornsodttir et al, 2015), and higher hospital admission and ED visits with HD as primary diagnosis (Finnbjornsodttir et al, 2016). A few interesting considerations need to be highlighted. In the studies of Kristbjornsdottir and Rafnsson (2013, 2012) there are indications of an exposure-response relationship, as the risk was higher when the geothermal area sub-cohort was compared to the cold area respect to the warm area. The authors also observed that the concomitant Rn exposure might have contributed to the observed risk associations, and not H_2S exclusively. In fact, Rn and its progeny are defined carcinogenic by the IARC because of evidence of an increased risk of lung cancer (IARC, 2001) and the IARC also stated that internalized radionuclides emitting alpha particles are carcinogenic to humans. However, a part of the inhaled Rn is absorbed into the blood and transported to all tissues and accumulated in higher concentrations in fatty tissues (IARC, 2001, Oestreicher et al, 2004); therefore, diverse tissues (including bone marrow) are exposed to alpha particles (IARC, 2001).

The strength of the studies of Kristbjornsdottir and Rafnsson (2015,2013, 2012) is the use of comprehensive population registries and the universal use of personal identification numbers while the principal limitation is the lack of individual exposure information on the mode and magnitude of ground gas emissions and components of the drinking water, as well as the composition of the hot water used for domestic heating and washing. The first two studies characterized by the exposure assessment (Carlsen et al, 2012; Finnbjornsdottir et al, 2015) relied on pollution measurements from only one measuring station in Reykjavik obtaining results though overall rather weak. More specifically, this monitoring station was used as a proxy for exposure of air pollutants although meteorological factors (e.g., wind speed and direction, cloud cover, precipitation and geographical distribution) are known to affect air pollution concentrations. This is especially true for H_2S concentrations depending on various meteorological factors; in fact, wind direction governs the direction of the plume and the neighborhoods situated closer to the geothermal harnessing site are likely to experience higher levels of exposure (Thorsteinsson et al, 2013; Ólafsdóttir et al, 2014). The study by Finnbjornsodttir et al. (2015) also presented a limited number of subjects and the authors recommended to interpret results with caution. In the study by Finnbjornsdottir et al. (2016) data exposure are derived from a simple model of H_2S exposure applied in five sections of the capital area, instead of containing data on individual exposure. Although this is also a limitation of the exposure assessment, nevertheless this approach is more advanced than the use of concentration measurements obtained from only one measurements station as in previous studies (Carlsen et al. 2012; Finnbjornsdottir et al. 2015).

The descriptive epidemiological Italian studies (Minichilli et al, 2012; Bustaffa et al, 2017) showed an overall health status of population living in geothermal areas not dissimilar from that of neighboring communities in particular in the NGA, since some excesses of mortality were observed in the SGA, especially in men (excesses for all cancers, particularly malignant neoplasm of liver and stomach). It is worth noting that both stomach and liver cancer are mainly attributable to other determinants, namely smoking, diet, inherited genetic conditions, *Helicobacter pylori* infection (Sauvaget et al, 2005; Hudler, 2012) and alcoholism, obesity-related fatty liver disease, and infections from hepatitis B and C (Gomaa et al, 2008), respectively, though the role of environmental pollution cannot be excluded. The greater concerns mainly observed in the male population in addition to a substantial non-alignment of mortality and hospitalization, were suggestive of an etiological role of occupational exposures or individual lifestyle. Indeed, in the NGA, where most geothermal power plants are located, few excesses of mortality were detected, some of them reasonably due to occupational factors, namely pneumoconiosis among men (Beer et al, 2017), while others are potentially associated to multiple risk factors, i.e., cerebrovascular disease among women (Bhatnagar, 2017), though not directly attributable to emissions of geothermal plants. On the other hand, the increased mortality for chronic liver disease and cirrhosis detected only in women of NGA in the study of Minichilli et al. (2012) and in both sexes residing in SGA (Bustaffa et al, 2017) can be largely attributable to viruses' infections and long-term alcohol abuse (Johnson and Gropman, 2007). Differently from studies performed in Italy and in other areas, the study of Nuvolone et al. (2019), aimed to evaluate health effects of the chronic exposure to low-level H_2S in SGA, reported an inverse association between H_2S exposure and risk for malignant neoplasms. By other side, coherently with previous Italian ecological surveys, excesses of mortality and hospitalization were observed for respiratory diseases, in particular for pneumonia, in both sexes. A decreased risk of mortality for ischemic HD, cerebrovascular diseases and acute myocardial infection, was found in relation to the elevation of H_2S exposure (Nuvolone et al, 2019), which in turn confirmed results of defects of mortality for ischemic HD found in Italian ecological researches (Minichilli et al, 2012; Bustaffa et al, 2017).

Recently H_2S, which represents the third endogenous gaseous mediator alongside nitrogen oxide and carbon monoxide for its modulatory effects in numerous physiological processes (Pan et al, 2017; Nandi et al, 2018), has been widely recognized as a cardiac protective agent for majority of cardiac disorders including myocardial ischemia/reperfusion injury, myocardial infarction, arrhythmias, cardiac hypertrophy, cardiac fibrosis, and heart failure (Shen et al, 2015). The molecular mechanisms by which H_2S protects against cardiac disease are multiple and involve prevention of inflammatory response, stimulation of angiogenesis, anti-oxidative action, anti-apoptosis, increased production of nitrogen oxide, regulation of ion channels and of microRNA expression (Shen et al, 2015; Pan et al, 2017). In contrast with these findings, the excess of mortality detected for heart failure and diseases of veins and lymphatics in Italy (Nuvolone et al, 2019) and the increased hospitalization for HD in Iceland (Finnbjornsdottir et al, 2016) could be the result of a complex interpretation of different patterns in cardiovascular diagnoses (Nuvolone et al, 2019). Compared to the precedent investigations conducted in Tuscany, characterized by the limitations proper of ecological studies, the exposure assessment used in this study, which was based on dispersion modeling, and an accurate match of H_2S exposure metrics with mortality and hospital discharge individual data, reduced the risk of information bias. On the other hand, though socio-economic status data was available at census tract level, individual information on lifestyle, diet and other potential confounding factors were not available. Furthermore, the time spent by each subject out of home was not assessed, thus H_2S levels estimated at residence might not adequately represent total exposure (Nuvolone et al, 2019).

Geothermal production of electricity and heat have been presented as one of the main alternative sources for energy production to avoid fossil fuels. The assessment of environmental effects and the compared cost benefit analysis are largely in favour of geothermal energy, in particular when the need for diffuse energy production and heating is considered (IRENA 2018). But the social acceptance of geothermal development is not straightforward. As depicted in a recent book analyzing 11 case studies where the linkage between society and use of geothermal energy is examined and detailed through sociological researches (Manzella et al, 2019a). The picture offered about the evolution of geothermal energy in those countries and the social studies undertaken accounts for a multiplicity of approaches and events, and some general conclusions can be drawn. It is possible to observe that the social acceptance of this kind of exploitation is often linked to the people's knowledge of environmental risks, and to their risk perception. The perception can be amplified by accidents happened and by the lack of trust in risk managers, or mitigated by dedicated information campaigns and by the public involvement in energy production choices. The association between environmental contamination and health is not mentioned, with the exception of Greece, Italy, New Zealand and Philippine, where citizen associations addressed this specific concern. In several cases the public controversies around geothermal energy use are not referred to possible specific health consequences, but to the quality of life in general, or environmental concerns. The cases presented provide some suggestions to understand a supposed lack of interest by public health and research institutions in tackling the health issues represented by geothermal energy for the communities. The role of communities has been and will be relevant in soliciting environmental health research and actions, as from a recent WHO report, "Citizens' demands for healthier environments will shape policy choices" (WHO, 2019).

Public consultations as part of the authorisation process are seldom in place, and public opinion often emerge in a conflictive mode; France has a National Commission for Public Debate (CNDP) (available at: *https://www.debatpublic.fr/*), in Italy a recent legislation introduced public debate in case of public Works above specific dimensions, as ancillary to the Environmental Impact Assessment, EIA, (available at: *http://biblus.acca.it/download/nuovo-codice-appalti-pdf/*); these regulations and the experience developed should be used to implement tools to promote the inclusion of stakeholders in public decisions.

It must be underlined also that geothermal prospection and exploitation is generally implemented by private enterprises and managed by governmental authorities in charge of energy production planning, underground resources like mines, public Works, transports and even internal affairs and security. The environmental competence is made explicit mainly in the monitoring phase at local level and during the authorization process, in particular in EIA that is binding for most of the plants in Europe. The updated version of the EIA Directive reinforced the inclusion of human health in the assessment, and authorization procedures like the integrated environmental authorization, IEA, often introduce obligations in the environmental health domain.

Considering those developments and the foreseen growth of the geothermal energy production, doubling the exploitation for energy production and five-folds growing for heating purposes, the potential health impacts on affected communities should be systematically taken into consideration.

5. Conclusions

The principal aim of this review is to draw conclusions about the health status of communities living in areas of geothermal exploitation. Results observed are heterogeneous and sometimes conflicting due both to the ecological nature of most of the studies and to the presence of confounding factors such as the presence of co-exposures difficult to evaluate (presence of PM_{10} or radon). Even a correct assessment of the exposure plays an important role in avoiding any biases as well as the complex sociological aspect of the geothermal exploitation should not be underestimated. In fact, there are actions or events that could mitigate or accentuate the knowledge and the perception of the risks the communities have about the geothermal exploitation. Consequently, communities can feel disoriented in the face of this phenomenon and their approach can consistently vary. Moreover, the geothermal resource is presented by private companies as a renewable source, an alternative to fossil fuel, but we described before how, for example, CO_2 emissions are not to be considered negligible. Finally, our review highlights that there are health effects deriving from the presence and/or the exploitation of the geothermal resource. Interesting signals emerge which will be the center of ongoing and future activities, such as acute and chronic respiratory outcomes and the cardiovascular health. The review is also presented to build a consensus on the more promising methodologies to proceed with a systematic evaluation of the health status of communities in areas of geothermal exploitation, which can accompany environmental assessments provided for the authorization procedures. In our opinion this can be achieved with the aid of integrated environment-health surveillance systems and through accurate exposure assessments. The monitoring systems should be wide and complex in order to take into account the different origin of the emissions (natural or industrial). The most suitable studies are the epidemiological cohort studies, possibly prospective, characterized by the continuous human biomonitoring of the communities living in geothermal areas. An application of these suggested methodologies, it is currently ongoing within the Italian project InVETTA, a human biomonitoring survey started in 2017, which is aimed at investigating the health status of population living in Mt. Amiata area, examining a sample of approximately 2,000 people. The study, which includes the collection of a blood and urine sample to determine the presence of heavy metals, the assessment of respiratory health by spirometry and an in-depth questionnaire on habits, living and working environment, personal medical history and risk perception, will be able to provide a deep insight on risk factors to health in geothermal areas.

To the best of our knowledge, this is the first example of integrated environment-health surveillance system on the health status of communities in geothermal areas and this application could also be recommended and used in the international context.

Author contribution

Conceptualization EB, FG, FM; Data curation EB, FG; Methodology EB, FG; Supervision AM, FB; Visualization AM, DN, EB, FB, FG, FM, LC; Writing - original draft EB, FG; Writing AM, EB, FG, LC; review & editing AM, DN, EB, FB, FG, FM, LC.

Declaration of competing interest

The authors declare no conflict of interest.

Funding

The research leading to these results has received funding from the European Union's Horizon 2020 Research and Innovation Program under grant agreement No 818242 (Project GEOENVI).

6. Bibliography

- ACGIH, American Conference of Governmental Industrial Hygienists, 2010. Hydrogen sulfide. Documentation of the Threshold Limit Values and Biological Exposure Indices. 7th edn. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists.

- Ármannsson, H., Fridriksson, T., Kristjánsson, B.R., 2005. CO_2 emissions from geothermal power plants and natural geothermal activity in Iceland. Geothermics 34, 286-296.
- Arnalds, Ó., 2010. Dust sources and deposition of aeolian materials in Iceland. Icel. Agric. Sci. 23, 3–21.
- ARPAT, Regional Agency for the Environmental Protection of Tuscany 2018. Monitoraggio delle aree geotermiche toscane. Monitoraggio ARPAT e validazione dati Enel, report anno 2018. Available: http://www.arpat.toscana.it/documentazione/report/report-geotermia/verifiche-autocontrollo-enel/concentrazione-h2s-e-hg-nelle-aree-geotermiche-validazione-dati-enel-anno-2017 (accessed 04 November 2019)
- ARPAT, Regional Agency for the Environmental Protection of Tuscany, 2015. Centrali geotermiche in Toscana. Available: http://www.arpat.toscana.it/temi-ambientali/sistemi-produttivi/impianti-di-produzione-di-energia/geotermia/centrali-geotermiche-in-toscana (accessed 04 November 2019)
- ATSDR, Agency for Toxic Substances and Disease Registry, 2016. Toxicological Profile for Hydrogen Sulphide. Division of Toxicology and Human Health Sciences, Environmental Toxicology Branch, Atlanta, Georgia. Available: https://www.atsdr.cdc.gov/toxprofiles/tp114.pdf (accessed 04 November 2019)
- Bates, M.N., Bailey, I.L., DiMartino, R.B., Pope, K., Crane, J., Garrett, N., 2017. Lens Opacity and Hydrogen Sulfide in a New Zealand Geothermal Area. Optom. Vis. Sci. 94(4): 487-495.
- Bates, M.N., Crane, J., Balmes, J.R., Garrett, N., 2015. Investigation of hydrogen sulfide exposure and lung function, asthma and chronic obstructive pulmonary disease in a geothermal area of New Zealand. PLoS One. 10(3): e0122062.
- Bates, M.N., Garrett, N., Crane, J., Balmes, J.R., 2013. Associations of ambient hydrogen sulfide exposure with self-reported asthma and asthma symptoms. Environ. Res. 122: 81–87.
- Bates, M.N., Garrett, N., Shoemack, P., 2002. Investigation of health effects of hydrogen sulfide from a geothermal source. Arch. Environ. Health. 57, 405-411.
- Bates, M.N., Garrett, N., Graham, B., Read, D., 1998. Cancer incidence, morbidity and geothermal air pollution in Rotorua, New Zealand. Int. J. Epidemiol. 27(1), 10-14.

- Bates, M.N., Garrett, N., Graham, B., Read, D., 1997. Air pollution and mortality in the Rotorua geothermal area. Aust. NZJ Public Health. 21(6), 581-586.
- Beer, C., Kolstad, H.A., Søndergaard, K., Bendstrup, E., Heederik, D., Olsen, K.E., Omland, Ø., Petsonk, E., Sigsgaard, T., Sherson, D.L., Schlünssen, V., 2017. A systematic review of occupational exposure to coal dust and the risk of interstitial lung diseases. Eur Clin Respir J. 4, 1264711. doi: 10.1080/20018525.2017
- Bertani, R., 2016. Geothermal power generation in the world 2010-2014 update report. Geothermics, 60, 31-43.
- Bhatnagar, A., 2017. Environmental Determinants of Cardiovascular Disease. Circ Res. 121, 162–180.
- Bravi, M., Basosi, R., 2014. Environmental impact of electricity from selected geothermal power plants in Italy. J. Clean. Prod. 66, 301-308.
- Bustaffa, E., Minichilli, F., Nuvolone, D., Voller, F., Cipriani, F., Bianchi, F., 2017. Mortality of populations residing in geothermal areas of Tuscany during the period 2003–2012. Ann. Ist. Super. Sanita 53, 108–117.
- Carlsen, H.K., Zoëga, H., Valdimarsdóttir, U., Gíslason, T., Hrafnkelsson, B., 2012. Hydrogen sulfide and particle matter levels associated with increased dispensing of anti-asthma drugs in Iceland's capital. Environ. Res. 113, 33-9.
- COP21. UN Climate Change Conference Paris 2015. Available: https://www.un.org/sustainabledevelopment/cop21/ (accessed 04 November 2019).
- Dickson, M.H., Fanelli, M., 2003. Geothermal Energy Utilization and Technology, Earthscan, London.
- Doll, R., 1991. Urban and rural factors in the aetiology of cancer. Int. J. Cancer. 47: 803–810.
- Dumas, P., 2019 Policy and Regulatory Aspects of Geothermal Energy: A European Perspective, in Manzella, A., Allansdottir, A., Pellizzone, A., (Eds.), Geothermal Energy and Society. Springer International Publishing, New York, pp. 19-37.
- Durand, M., Scott, B.J., 2005 Geothermal ground gas emissions and indoor air pollution in Rotorua, New Zealand. Sci. Total Environ. 345, 69-80.

- Durand, M., Scott, B.J., 2003. An investigation of geothermal soil gas emissions and indoor air pollution in selected Rotorua buildings. Institute of geological and nuclear sciences, Lower Hutt, New Zealand, 2003.
- Durand, M., Wilson, G.J., 2006. Spatial analysis of respiratory disease on an urbanized geothermal field. Environ. Res. 101: 238–245.
- Elliott, P., Wakefield, J.C., Best, N.G., Briggs, D.J., 2000. Spatial epidemiology, methods and applications, Oxford University Press, Oxford.
- EU Energy2030. 2030 climate & energy framework. Available: https://ec.europa.eu/clima/policies/strategies/2030_en (accessed 04 November 2019)
- Faller, S. Ryter, S.W., Choi, A.M., Loop, T., Schmidt, R., Hoetzel, A., 2010. Inhaled hydrogen sulphide protects against ventilator-induced lung injury. Anesthesiology 113, 104-115.
- Fisher, G.W., 1999. Natural levels of hydrogen sulphide in New Zealand. Atmos. Environ. 33, 3078-3079.
- Finnbjornsdottir, R.G., Carlsen, H.K., Thorsteinsson, T., Oudin, A., Lund, S.H., Gislason, T., Rafnsson, V., 2016. Association between Daily Hydrogen Sulfide Exposure and Incidence of Emergency Hospital Visits: A Population-Based Study. PLoS One. 11(5), e0154946.
- Finnbjornsdottir, R.G., Oudin, A., Elvarsson, B.T., Gislason, T., Rafnsson, V., 2015. Hydrogen sulfide and traffic-related air pollutants in association with increased mortality: a case-crossover study in Reykjavik, Iceland. BMJ Open. 5(4), e007272.
- Fridleifsson, I.B., 1979. Geothermal activity in Iceland. Jökull 29, 47–56.
- Giggenbach, W.F., 1997. Relative importance of thermodynamic and kinetic processes in governing the chemical and isotopic composition of carbon gases in high-heatflow sedimentary basins. Geochim Cosmochim. Acta 61, 3763-3785.
- Gomaa, A.I., Khan, S.A., Toledano, M.B., Waked, I., Taylor-Robinson, S.D., 2008. Hepatocellular carcinoma: epidemiology, risk factors and pathogenesis. World J. Gastroenterol. 14, 4300-4308.
- Haraldsson, I.G., Ketilsson, J., 2010. Frumorkunotkun jarð a varmavirkjana og hitaveitna á Íslandi til ársins 2009. (Geothermal primary energy production for electricity generation and heating in Iceland up to year 2009). OS-2010/03. Reykjavik Orkustofnun.

- Horwell, C., 1998. Geothermal hydrogen sulfide mapping across Rotorua, New Zealand: implications for the assessment of public health. Thesis, Dipl Appl Science (Vulcanology), School of Earth Sciences, Victoria University of Wellington, New Zealand.
- Horwell, C.J., Patterson, J.E., Gamble, J.A., Allen, A.G., 2005. Monitoring and mapping of hydrogen sulphide emissions across an active geothermal field: Rotorua, New Zealand. Journal of Vulcanology and Geothermal Research 139, 259-269.
- Hudler, P., 2012. Genetic aspects of gastric cancer instability. ScientificWorldJournal. 2012, 761909. doi: 10.1100/2012/761909
- IARC, International Agency for Research on Cancer. Ionizing radiation, part 2: some internally deposited radionuclides. Views and expert opinions of an IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 14-21 June 2000. IARC Monogr Eval Carcinog Risks Hum 2001 78:1-599.
- IPCS, International Programme on Chemical Safety, 1981. Hydrogen Sulfide. Geneva: World Health Organization.
- IPCC, Intergovernmental Panel on Climate Change, 2012. Renewable energy sources and climate change mitigation: special report of the intergovernmental panel on climate change. New York.
- ISTAT, 2019. Available at https://www.istat.it/it/dati-analisi-e-prodotti/banche-dati (accessed 04 November 2019).
- Johnson, D., Groopman, J.D., 2007. Toxic liver disorders, in: Rom, W.N., Markovitz, S., (Eds), Environmental and occupational medicine, 4th ed. Lippincott Williams & Wilkins, Philadelphia.
- Jóhannsson, T. 2007. Particle Pollution in Reykjavik [In Icelandic]. M. Sc. Thesis. University of Iceland, Reykjavik, Iceland. Available: http://www2.hi.is/page/ msub070Bs (accessed 15 July 2019).
- King, A.L., Lefer, D.J., 2011. Cytoprotective actions of hydrogen sulfide in ischaemia-reperfusion injury. Exp. Physiol. 96, 840-846.
- Kristbjornsdottir, A., Aspelund, T., Rafnsson, V., 2016. Association of Cancer Incidence and Duration of Residence in Geothermal Heating Area in Iceland: An Extended Follow-Up. PLoS ONE 11, e0155922. doi: 10.1371/journal.pone.0155922.

- Kristbjornsdottir, A., Rafnsson, V., 2015. Cancer mortality and other causes of death in users of geothermal hot water. Acta Oncol. 54(1): 115-123.
- Kristbjornsdottir, A., Rafnsson, V., 2013. Cancer incidence among population utilizing geothermal hot water: a census-based cohort study. Int. J. Cancer. 133(12): 2944-2952.
- Kristbjornsdottir, A., Rafnsson V., 2012. Incidence of cancer among residents of high temperature geothermal areas in Iceland: a census based study 1981 to 2010. Environ.Health. 11: 73.
- Kristmannsdóttir, H., Ármannsson, H., 2003. Environmental aspects of geothermal energy utilization. Geothermics 32, 451–61.
- Lattanzi, P., Beutel, M.W., Costagliola, P., Fagotti, C., Rimondi V., 2019. Tracing the impact of geothermal plants in the Monte Amiata area, Tuscany, Italy: evidence from Hg contents in stream sediments and tree barks. Proc. European Geothermal Congress, Den Haag, The Netherlands, 11-14 June 201.
- Lund, J.W., Boyd, T.L., 2016. Direct utilization of geothermal energy 2015 worldwide review. Geothermics 60, 66–93.
- Manzella A., Allansdottir, A., Pellizzone, A., 2019a. Geothermal Energy and Society., Springer International Publishing, New York.
- Manzella A., Serra D., Cesari G., Bargiacchi E., Cei M., Cerutti P., Conti P., Giudetti G., Lupi M., Vaccaro M., 2019b. Geothermal Energy Use, Country Update for Italy. Proceedings of European Geothermal Congress 2019 Den Haag, The Netherlands, 11-14 June 2019.
- Manzella, A., R. Bonciani, Allansdottir, A., Botteghi, S., Donato, A., Giamberini, S., Lenzi, A., Paci, M., Pellizzone, A., Scrocca, D., 2018. Environmental and social aspects of geothermal energy in Italy. Geothermics, 72, 232-248.
- Menichini, F., Mudu, P., 2010. Drug consumption and air pollution: an overview. Pharmacoepidemiol. Drug Saf. 19, 1300–1315.
- Minichilli, F., Nuvolone, D., Bustaffa, E., Cipriani, F., Vigotti, M.A., Bianchi, F., 2012. [State of health of populations residing in geothermal areas of Tuscany]. Epidemiol. Prev. 36(5), 1-104. Italian.

- Nandi, S., Ravindran, S., Kurian, G.A., 2018. Role of endogenous hydrogen sulfide in cardiac mitochondrial preservation during ischemia reperfusion injury. Biomed Pharmacother. 97, 271-279.
- Naureckas, E.T., Dukic, V., Bao, X., Rathouz, P., 2005. Short-acting beta-agonist prescription fills as a marker for asthma morbidity. Chest 128, 602–608.
- Nuvolone, D., Petri, D., Pepe, P., Voller, F., 2019. Health effects associated with chronic exposure to low-level hydrogen sulfide from geothermoelectric power plants. A residential cohort study in the geothermal area of Mt. Amiata in Tuscany. Sci Total Environ, 659, 973-982.
- Oestreicher, U., Braselmann, H., Stephan, G., 2004. Cytogenetic analyses in peripheral lymphocytes of persons living in houses with increased levels of indoor radon concentrations. Cytogenet. Genome Res. 104, 232-236.
- Olafsdottir AO, Sigurdardottir H. Reykjavik's Energy's environmental report 2013 [in Icelandic]. Reykjavik: Reykjavik Energy, 2013.
- Olson, K.R., Donald, J.A., 2009. Nervous control of circulation – the role of gastrotransmitters, NO, CO, and H2S. Acta Histochem. 111, 244-256.
- Pan, L.L, Qin, M., Liu, X.H., Zhu, Y.Z., 2017. The Role of Hydrogen Sulfide on Cardiovascular Homeostasis: An Overview with Update on Immunomodulation. Front Pharmacol. 8, 686. doi: 10.3389/fphar.2017.00686
- Pearce, N. 2000. The ecological fallacy strikes back. J. Epidemiol. Community Health, 54, 326-327.
- Pope, K., So, Y.T., Crane, J., Bates, M.N., 2017. Ambient geothermal hydrogen sulfide exposure and peripheral neuropathy. Neurotoxicology 60, 10-15.
- Reed, B.R., Crane, J., Garrett, N., Woods, D.L., Bates, M.N., 2014. Chronic ambient hydrogen sulfide and cognitive function. Neurotoxicol. Teratol. 42, 68-76.
- Saemundsson, K., 1979. Outline of the geology of Iceland. Jökull 29, 7–28.
- Sauvaget, C., Lagarde, F., Nagano, J., Soda, M., Kojama, K., Kodama, K., 2005. Lifestyle factors, radiation and gastric cancer in atomic-bomb survivors (Japan). Cancer Causes Control 16, 773–780.
- Schwartz M., 1994. The fallacy of ecological fallacy: the potential misuse of a concept and consequences. Am. J. Public Health 84, 819-823.

- Scott B., 2019. The Science Story. Environmental Summary Report. Rotorua Geothermal System. Available at https://atlas.boprc.govt.nz/api/v1/edms/document/A3331002/content (accessed 04 November 2019).
- Shen, Y., Shen, Z., Luo, S., Guo, W., Zhu, Y.Z., 2015. The Cardioprotective Effects of Hydrogen Sulfide in Heart Diseases: From Molecular Mechanisms to Therapeutic Potential. Oxid Med Cell Longev. 2015, 925167. doi: 10.1155/2015/925167
- Shortall, R., Davidsdottir, B., Axelssonc, G., 2015. Geothermal energy for sustainable development: a review of sustainability impacts and assessment frameworks. Renew. Sust. Energ. Rev. 44, 391–406.
- The Economist Group, 2008. Pocket World in Figures 2009. Economist Books, London.
- The World Bank Group. Motorvehicles (per 1,000 people) 2014 [cited 2014 July 22]. World Bank Open Data: free and open access to data about development in countries around the globe. Available: http://data.worldbank.org/indicator/IS.VEH.NVEH.P3/countries/1W-IS?display=default (accessed 04 November 2019)
- Thorsteinsson, T., Hackenbruch, J., Sveinbjörnsson, E., Jóhannsson T., 2013. Statistical assessment and odeling of the effects of wather conditions on H2S plume dispersal from Icelandic geothermal plants. Getohermics. 1:43-46.
- UHR, The Reykjavik Municipality Department of the Environment, 2007. Measurements of Air Pollutants in Reykjavik 2006 [In Icelandic]. Annual Report. The Reykjavik Municipality Department of the Environment.
- Whiteman, M., Le Trionnaire, S., Chopra, M., Fox, B., Whatmore, J., 2011. Emerging role of hydrogen sulfide in health and disease: critical appraisal of biomarkers and pharmacological tools. Clin. Sci. (Lond.) 121, 459-488.
- WHO, 2000. Air Quality Guidelines for Europe. 2nd ed. vol. 91. WHO Regional Publications. Available: http://www.euro.who.int/__data/assets/pdf_file/0005/74732/E71922.pdf (accessed 04 November 2019)

- WHO, 2019. Health, environment and climate change, Draft WHO global strategy on health, environment and climate change, Seventy-Second World Health Assembly, 18 April 2019. Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_15-en.pdf (accessed 04 November 2019).

Table
Click here to download Table: Tables1-2.docx

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered.

Study Design	Study sample	Study Period	Exposure	Outcomes (ICD IX code)	Results (95%CI)	Confounders	Reference
NEW ZEALAND							
Ecological	n.d.	1981-1990	n.d.	Disease of the circulatory system (390-459)	SMR=0.94 (0.90-0.99) p=0.02	Age Calendar year Sex Ethnicity	Bates et al, 1997
				Acute rheumatic fever and chronic rheumatic heart disease (390-398)	SMR=1.51 (1.06-2.08) p=0.01		
				Hypertensive disease (401-405)	SMR=1.61 (1.24-2.05) p<0.001		
				Other heart disease (420-429)	SMR=0.70 (0.58-0.84) P<0.001		
				Diseases of the respiratory system (460-519)	SMR=1.18 (1.08-1.29) p<0.001		
				Pneumonia and influenza (480-487)	SMR=1.20 (1.04-1.38) p=0.008		
				Chronic obstructive respiratory disease and allied conditions (490-496)	SMR=1.20 (1.06-1.35) p=0.004		
				Disease of the circulatory system (390-459)	*Other (men)* SMR=0.91 (0.84-0.97) p=0.007	Age Calendar year	
				Diseases of the respiratory system (460-519)	*Maori (women)* SMR=1.61 (1.19-2.12) p=0.001		
Ecological	n.d.	1981-1990	n.d.	***Cancer*** Upper lobe, bronchus or lung (162.3)	SIR=0.65 (0.49-0.83) p=0.001	Age Calendar year Sex Ethnicity	Bates et al, 1998
				Bronchus and lung unspecified (162.9)	SIR=1.45 (1.13-1.84) p=0.002		
				Discharge Diseases of the nervous system and sense organs (320-389)	SIR=1.11 (1.07-1.15) p<0.001		
				Other disorders of the central nervous system (340-349)	SIR=1.35 (1.21-1.51) p<0.001		
				Infantile cerebral palsy (343)	SIR=1.42 (1.03-1.89) p=0.02		
				Migraine (346)	SIR=1.40 (1.12-1.72) p=0.002		
				Other conditions of brain (348)	SIR=2.50 (1.89-3.26) p<0.001		
				Disorders of the peripheral nervous system (350-359)	SIR=1.22 (1.11-1.33) p<0.001		
				Mononeuritis of upper limb and mononeuritis multiplex (354)	SIR=1.47 (1.29-1.67) p<0.001		
				Mononeuritis of lower limb (355)	SIR=2.06 (1.46-2.81) p<0.001		
				Disorders of the eye and adnexa (360-379)	SIR=1.12 (1.05-1.19) p<0.001		
				Cataract (366)	SIR=1.26 (1.14-1.38) p<0.001		
				Disorders of conjunctiva (372)	SIR=2.09 (1.66-2.59) p<0.001		
				Disorders of the orbit	SIR=1.69 (1.12-2.44) p=0.005		
				Hypertensive disease (401-405)	SIR=1.15 (1.00-1.32) p=0.05		
				Diseases of pulmonary circulation (415-417)	SIR=0.72 (0.54-0.93) p=0.01		
				Other heart disease (420-429)	SIR=1.06 (1.00-1.13) p=0.04		
				Cerebrovascular disease (430-438)	SIR=0.85 (0.79-0.91) p<0.001		
				Diseases of arteries, arterioles & capillaries (440-448)	SIR=1.17 (1.07-1.28) p=0.001		
				Diseases of veins & lymphatics & other circulatory diseases (451-459)	SIR=1.22 (1.15-1.29) p<0.001		
				Diseases of the respiratory system (460-519)	SIR=1.05 (1.02-1.07) p=0.001		
				Acute respiratory infections (460-466)	SIR=0.88 (0.83-0.93) p<0.001		
				Other diseases of the upper respiratory tract (470-478)	SIR=1.27 (1.20-1.33) p<0.001		
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	***Discharge*** **Diseases of the nervous system and sense organs (320-389)**	High: SIR=2.19 (1.99-2.41) Medium: SIR=1.31 (1.17-1.47) Low: SIR=1.23 (1.16-1.30) ptrend<0.001	Age Gender Ethnicity	Bates et al, 2002
				Other disorders of the central nervous system (340-349)	High: SIR=2.68 (2.01-3.50) Medium: SIR=1.67 (1.20-2.27) Low: SIR=1.38 (1.16-1.63) ptrend<0.001		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcomes (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	Disorders of the eye and adnexa (360-379)	High: SIR=2.27 (1.97-2.61) Medium: SIR=1.57 (1.30-1.89) Low: SIR=1.47 (1.33-1.63) ptrend<0.001	Age Gender Ethnicity	Bates et al, 2002
				Disorders of the ear and mastoid process (380-389)	High: SIR=2.00 (1.64-2.40) Medium: SIR=1.01 (0.83-1.21) Low: SIR=0.99 (0.91-1.08) ptrend<0.001		
				Disease of the circulatory system (390-459)	High: SIR=1.39 (1.29-1.50) Medium: SIR=0.95 (0.86-1.06) Low: SIR=1.08 (1.02-1.13) ptrend<0.001		
				Ischemic heart disease (410-414)	High: SIR=1.53 (1.35-1.73) Medium: SIR=0.89 (0.73-1.06) Low: SIR=1.20 (1.11-1.30) ptrend=0.02		
				Cerebrovascular disease (430-438)	High: SIR=1.14 (0.94-1.38) Medium: SIR=1.03 (0.80-1.31) Low: SIR=0.85 (0.74-0.97) ptrend=<0.01		
				Diseases of arteries, arterioles and capillaries (440-448)	High: SIR=1.66 (1.30-2.09) Medium: SIR=1.58 (1.17-2.08) Low: SIR=1.08 (0.90-1.29) ptrend<0.001		
				Diseases of the respiratory system (460-519)	High: SIR=1.65 (1.51-1.79) Medium: SIR=1.03 (0.94-1.14) Low: SIR=1.11 (1.06-1.16) ptrend<0.001		
				Acute respiratory infections (460-466)	High: SIR=1.77 (1.43-2.16) Medium: SIR=0.86 (0.69-1.05) Low: SIR=1.12 (1.02-1.22) ptrend=0.02		
				Other diseases of the upper respiratory tract (470-478)	High: SIR=1.98 (1.58-2.45) Medium: SIR=1.68 (1.39-2.01) Low: SIR=1.48 (1.34-1.63) ptrend=0.01		
				Pneumonia and influenza (480-487)	High: SIR=1.56 (1.31-1.85) Medium: SIR=1.02 (0.83-1.25) Low: SIR=1.09 (0.99-1.20) ptrend=0.002		
				Chronic obstructive respiratory disease and allied conditions (490-496)	High: SIR=1.57 (1.32-1.86) Medium: SIR=0.82 (0.66-1.02) Low: SIR=0.93 (0.84-1.03) ptrend<0.001		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcomes (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	n.d.	1993-1996	Exposure to H_2S high/medium/low on the basis of the degree of darkening of the photographic paper in the passive samplers	Other diseases of the respiratory system (510-519)	High: SIR=1.51 (1.15-1.94) Medium: SIR=0.96 (0.68-1.34) Low: SIR=0.97 (0.82-1.14) ptrend=0.008	Age Gender Ethnicity	Bates et al, 2002
Spatial cluster analysis	12,215 visits	1991-2000	H_2S concentration High ~1 ppm Medium ~500 ppb Low ~30-40 ppb	Diseases of the respiratory system (460-519)	1: RR=5.1; 2: RR=5.9	1: Age; Smoking; Deprivation 2: Ethnicity; Smoking; Deprivation	Durand and Wilson, 2006
				Other diseases of the upper respiratory system (470-478)	1: RR=8.7; 2: RR=8.2		
				Chronic obstructive pulmonary disease (490-496)	1: RR=5.1; 2: RR=6.1		
				Asthma (493)	1: RR=7.6; 2: RR=10.5		
				Symptoms involving respiratory system and other chest symptoms	1: RR=7.9; 2: RR=11.8		
ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Cohort	74,806 individuals aged 5-65 GA 1,497 WRA 50,878 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.16 (1.00-1.34) CRA: HR=1.22 (1.05-1.42)	Age Gender Education Type of housing	Kristbjornsdottir and Rafnsson, 2012
				Pancreas (C25)	*Men+Women* WRA: HR=2.57 (1.30-5.07) CRA: HR=2.85 (1.39-5.86) *Men* WRA: HR=2.52 (1.01-6.28) CRA: HR=3.66 (1.37-9.82)		
				Bone (C40-C41)	*Women* WRA: HR=7.95 (1.70-37.23) CRA: HR=7.20 (1.30-39.96)		
				Breast (C50)	*Men+Women* WRA: HR=1.43 (1.00-2.05) CRA: HR=1.59 (1.10-2.31) *Women* WRA: HR=1.46 (1.02-2.09) CRA: HR=1.62 (1.12-2.36)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men+Women* CRA: HR=1.64 (1.00-2.66)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men+Women* WRA: HR=3.21 (1.77-5.82) CRA: HR=3.25 (1.73-6.07) Men WRA: HR=3.12 (1.43-6.78) CRA: HR=2.58 (1.16-5.78) *Women* WRA: HR=3.31 (1.32-8.34) CRA: HR=5.20 (1.87-14.45)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Cohort	74,806 individuals aged 5-65 GA 1,497 WRA 50,878 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	Basal cell carcinoma of the skin (Not included in all cancers)	*Men+Women* CRA: HR=1.61 (1.10-2.35) Men CRA: HR=1.78 (1.04-3.05)	Age Gender Education Type of housing	Kristbjornsdottir and Rafnsson, 2012
Census-based cohort study	73,309 individuals aged 5-64 HWSA 6,014 WRA 44,864 CRA 22,431	1981-2010	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.10 (1.01-1.20) CRA: HR=1.15 (1.05-1.25) *Men* WRA: HR=1.14 (1.01-1.27) CRA: HR=1.22 (1.08-1.37)	Age Gender Education Type of housing Smoking habits	Kristbjornsdottir and Rafnsson, 2013
				Oesophagus (C15)	*Men* CRA: HR=3.34 (1.35-8.26)		
				Breast (C50)	*Men+Women* WRA: HR=1.28 (1.04-1.59) CRA: HR=1.40 (1.12-1.75) *Women* WRA: HR=1.27 (1.02-1.58) CRA: HR=1.38 (1.11-1.73)		
				Prostate (C61)	*Men* WRA: HR=1.48 (1.21-1.82) CRA: HR=1.61 (1.29-2.00)		
				Kidney (C64-C66)	*Men and women* WRA: HR=1.51 (1.05-2.18) CRA: HR=1.64 (1.11-2.41) *Men* CRA: HR=1.76 (1.08-2.86)		
				Brain and central nervous system (C70-C72, C75.1 and C75.3)	*Men and women* WRA: HR=0.56 (0.32-0.98)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men and women* WRA: HR=1.51 (1.05-2.18) CRA: HR=1.64 (1.11-2.41) *Women* CRA: HR=1.66 (1.06-2.58)		
				Non-Hodgkin's lymphoma (C82-C85)	*Women* CRA: HR=2.50 (1.07-5.83)		
				Basal cell carcinoma of the skin (Not included in all cancers)	*Men and women* WRA: HR=1.24 (1.01-1.54) CRA: HR=1.46 (1.16-1.82) *Men* CRA: HR=1.46 (1.05-2.04) *Women* CRA: HR=1.43 (1.06-1.93)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Exposure**	**Cancers (ICD X code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	74806 individuals aged 5-64 GA 7511 WRA 44864 CRA 22431	1981-2009	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	Breast (C50)	*Women* RA: HR=1.49 (1.06-2.09)	Age Education Type of housing Smoking habits	Kristbjornsdottir and Rafnsson, 2015
				Prostate (C61)	*Men* RA: HR=1.88 (1.37-2.60)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men* RA: HR=2.31 (1.21-4.41)		
Population based cohort study	74806 individuals aged 5-64 GA 7511 WRA 44864 CRA 22431	1981-2013	Warm area (bedrock 3.3 million years old; <150°C at 1,000 m depth) Cold area (bedrock dates from different period)	All sites (C00-C97 and D45-D47)	*Men+Women* WRA: HR=1.10 (1.02-1.18) CRA: HR=1.21 (1.12-1.30) *Men+Women (5-years lat.)* WRA: HR=1.16 (1.03-1.30) CRA: HR=1.22 (1.08-1.37)	Age Gender Education Type of housing Smoking habits **HR with stratification into categories of cumulative years of residence**	Kristbjornsdottir et al, 2016
				Pancreas(C25)	*Men+Women* WRA: HR=1.53 (1.00-2.32) CRA: HR=1.93 (1.22-3.06) *Men+Women (5-years lat.)* WRA: HR=2.11 (1.03-4.34)		
				Breast (C50)	*Men+Women* WRA: HR=1.27 (1.07-1.52) CRA: HR=1.48 (1.23-1.80)		
				Prostate (C61)	WRA: HR=1.32 (1.11-1.57) CRA: HR=1.47 (1.22-1.77)		
				Kidney (C64-C66)	*Men+Women* CRA: HR=1.46 (1.03-2.05)		
				Lymphoid and haematopoietic tissue (C81-C96 and D45-D47)	*Men+Women* WRA: HR=1.36 (1.08-1.72) CRA: HR=1.54 (1.21-1.97) *Men+Women (5-years lat.)* WRA: HR=1.61 (1.10-2.36) CRA: HR=1.70 (1.14-2.55)		
				Non-Hodgkin's lymphoma (C82-C85)	*Men+Women* WRA: HR=1.90 (1.30-2.77) CRA: HR=2.08 (1.38-3.15) *Men+Women (5-years lat.)* WRA: HR=2.30 (1.27-4.14) CRA: HR=3.02 (1.52-6.00)		
				Basal cell carcinoma of the skin (C44)	WRA: HR=1.28 (1.08-1.52) CRA: HR=1.62 (1.35-1.94) *Men+Women (5-years lat.)* CRA: HR=1.48 (1.12-1.96)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcome (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	Average resident population in Geothermal Area: 43,440 subjects (16,902 in NGA and 26,358 in SGA). 21,031 Men 22,409 Women	2000-2006	--	***Mortality*** All causes (0-999)	*TGA* - M: SMR=108 (103-112) *SGA* - M: SMR=115 (109-121)	Deprivation index	Minichilli et al, 2012
				Infectious and parasitic diseases (001-139)	*TGA* - M: SMR=245 (159-362) *SGA* - M: SMR=250 (125-447)		
				Neoplasms (140-239)	*NGA* - M: SMR=87 (76-98) *SGA* - M: SMR=121 (110-131)		
				Malignant neoplasm of liver and intrahepatic bile ducts (155)	*TGA* - M: SMR=138 (104-179) *SGA* - M: SMR=171 (122-234)		
				Malignant neoplasm of trachea, bronchus, and lung (162)	*SGA* - M: SMR=121 (101-145)		
				Malignant neoplasm of ovary and other uterine adnexa (183)	*NGA* - W: SMR=172 (100-275)		
				Disorders of the nervous system and sense organs (320-389)	*TGA* - M: SMR=130 (101-163)		
				Ischemic heart disease (410-414)	*TGA* - W: SMR=85 (74-97)		
				Cerebrovascular disease (430-438)	*NGA* - W: SMR=122 (104-142)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SMR=129 (112-147) *SGA* - M: SMR=132 (110-157)		
				Acute respiratory infections (460-466)	*SGA* - W: SMR=142 (102-193)		
				Pneumoconiosis (500-505)	*TGA* - M: SMR=372 (277-489) *NGA* - M: SMR=351 (214-542) *SGA* - M: SMR=388 (263-550)		
				Diseases of the digestive system (520-579)	*SGA* - W: SMR=130 (102-164)		
				Chronic liver disease and cirrhosis (571)	*NGA* - W: SMR=143 (100-199)		
				Hospitalization All causes (0-999)	*NGA* - W: SHR=106 (100-111)		
				Malignant neoplasm of stomach (151)	*TGA* - W: SHR=153 (110-206) *SGA* - W: SHR=161 (108-231)		
				Malignant neoplasm of liver and intrahepatic bile ducts (155)	*SGA* - M: SHR 160 (101-240)		
				Malignant neoplasm of lymphatic and hematopoietic tissue (200-208)	*TGA* - W: SHR=139 (102-186)		
				Leukemia (204-208)	*TGA* - W: SHR=262 (131-469) *NGA* - W: SHR=181 (109-283)		
				Parkinson's disease (332)	*SGA* - M: SHR=227 (109-418)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SHR=111 (103-120) *SGA* - M: SHR=116 (105-128) W: SHR=122 (110-136)		
				Diseases of the digestive system (520-579)	*NGA* - M: SHR=112 (101-124) W: SHR=112 (100-125)		
				Acute and chronic renal failure (584-585)	*SGA* - M: SHR=150 (115-193) W: SHR=153 (114-200)		
				Congenital heart disease	*NGA*: O/E: 43 (14-99)		
				Urogenital anomalies	*SGA*: O/E: 210 (109-367)		
				Low-birth weight	*SGA*: O/E: 72 (53-95)		
				Gestational age <37 weeks	O/E: 75 (57-98)		

Table 1. Epidemiological studies based on health indicators, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Exposure**	**Outcome (ICD IX code)**	**Results (95%CI)**	**Confounders**	**Reference**
Ecological	Average resident population in Geothermal Area: 40,461 subjects (16,630 in NGA and 23,831 in SGA). 19,678 Men 20,784 Women	203-2012	--	All causes (0-999)	*TGA* – M: SMR=103 (100-107) *SGA* - M: SMR=109 (104-114)	Deprivation index	Bustaffa et al, 2017
				Neoplasms (140-239)	*NGA* - M: SMR=86 (77-95) *SGA* - M: SMR=116 (107-125)		
				Malignant neoplasm of stomach (151)	*SGA* - M: SMR=146 (114-185)		
				Malignant neoplasm of liver, gallbladder and bile ducts (155,156)	*SGA* - M: SMR=153 (116-199)		
				Malignant neoplasm of trachea, bronchus, and lung (162)	*NGA* - M: SMR=72 (56-91)		
				Malignant neoplasm of breast (174-175)	*TGA* - W: SMR=77 (61-97)		
				Malignant neoplasm of ovary and other uterine adnexa (183)	*TGA* - *W*: SMR=138 (102-183) *NGA* - W: SMR=164 (103-248)		
				Malignant neoplasm of lymphatic and hematopoietic tissue (200-208)	*SGA* - M: SMR=69 (47-97)		
				Malignant neoplasm of the central nervous system (191-192, 225, 239.6)	*TGA* – W: SMR=148 (104-203) *SGA* - W: SMR=184 (123-264)		
				Diseases of the circulatory system (390-459)	*SGA* - M: SMR=91 (84-99) W: SMR=93 (87-99)		
				Ischemic heart disease (410-414)	*TGA* - W: SMR=81 (73-91) *SGA* - M: SMR=79 (68-91) W: SMR=76 (65-88)		
				Cerebrovascular disease (430-438)	*NGA* - W: SMR=115 (101-132)		
				Diseases of the respiratory system (460-519)	*TGA* - M: SMR=134 (120-149) *NGA* - M: SMR=132 (111-155) *SGA* - M: SMR=135 (117-155)		
				Acute respiratory infections (460-466)	*SGA* - W: SMR=142 (107-186)		
				Pneumonia (487)	*SGA* - W: SMR=137 (100-184)		
				Chronic obstructive pulmonary disease (491-492, 494-496)	*TGA* - M: SMR=119 (101-139)		
				Pneumoconiosis (500-505)	*TGA* - M: SMR=325 (258-406) *NGA* - M: SMR=364 (256-502) *SGA* - M: SMR=298 (215-402)		
				Diseases of the digestive system (520-579)	*TGA* - W: SMR=134 (114-155) *SGA* - M: SMR=127 (101-157) W: SMR=147 (121-176)		

Notes – n.d.: not defined; ICD: International Classification of Disease; 95%CI: 95% Confidence Interval; SMR: Standardized Mortality Ratio; SIR: Standardized Incidence Ratio; H_2S: Hydrogen Sulfide; ppm: part per million; ppb: part per billion; RR: Relative Risk; GA: Geothermal Area; WRA: Warm Reference Area; CRA: Cold Reference Area; HR: Hazard Ratio; HWSA: Hot Water Supply Area; RA: Reference Area; TGA: Total Geothermal Area; NGA: Northern Geothermal Area; SGA: Southern Geothermal Area; M: men; W: women; SHR: Standardize Hospitalization Ratio; O/E: Observed/Expected.

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered.

NEW ZEALAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Cross-sectional	1637 subjects aged 18-65	2008-2010	Wheeze or whistling	**Prevalence ratio by quartile (Q) of maximum H_2S exposure concentrations** Q2 Vs Q1 0.98 (0.81-1.19) Q3 Vs Q1 0.87 (0.71-1.08) Q4 Vs Q1 0.80 (0.65-0.99) ptrend=0.02	Estimated from data collected by summer and winter H_2S monitoring networks. Median H_2S concentration 0-64 ppb (averaged between winter and summer): for residences 20.3 ppb (mean 20.8 ppb) and for workplaces 26.4 ppb (median 27.7 ppb). Calculation of four metrics for H_2S exposure, representing current and long term exposure and TWM exposure and MWH. For TWM exposure: Q1 (0-10 ppb) as reference Q2 (11-20 ppb) Q3 (21-30 ppb) Q4 (31-64 ppb) For MWH exposure: Q1 (0-10 ppb) as reference Q2 (11-20 ppb) Q3 (30-44 ppb) Q4 (45-64 ppb)	Sex Smoking habits Age Ethnicity Education level Employment status	Bates et al, 2013
Cross-sectional	1637 subjects aged 18-65 having lived in Rotorua for at least the last 3 years	2008-2010	Attention, psychomotor speed, memory, fine motor skills, mood	**No association between H_2S exposure and cognitive function.** **Slightly better performance of simple reaction time and digit correct symbol for higher levels of H_2S (Q4) both for current (a) and long term (b) exposure and both for time-weighted mean (TWM) exposure and maximum exposure at work or home (MWH).** <u>Simple reaction time (a)</u> TWM Q4 Vs Q1 -2.3 (-6.3-1.6) MWH Q4 Vs Q1 -4.1 (-8.0-(-0.1)) <u>Digit symbol correct (a)</u> TWM Q4 Vs Q1 1.1 (-0.4-2.5) MWH Q4 Vs Q1 1.2 (-0.2-2.7) <u>Simple reaction time (b)</u> TWM Q4 Vs Q1 -1.8 (-5.9-2.2) MWH Q4 Vs Q1 -3.0 (-7.1-1.1) <u>Digit symbol correct (b)</u> TWM Q4 Vs Q1 0.7 (-0.8-2.2) MWH Q4 Vs Q1 0.6 (-0.9-2.1)		Age Sex Ethnicity Education Income Alcohol consumption, NART Examiner	Reed et al, 2014
Cross-sectional	1,204 subjects aged 18-65 414 men 790 women	2008-2010	Asthma and Chronic Obstructive Pulmonary Disease (COPD)	**No evidence (for all participants combined and all subgroups) of an adverse association between the ambient H_2S levels in Rotorua and any of the spirometric parameters examined or COPD**		Sex Smoking habits Age Ethnicity Education level Employment status Income	Bates et al, 2015
Cross-sectional	1,637 subjects aged 18-65	---	4 outcome categories to assess lens opacity (based on LOCS score) Nuclear Opacity Nuclear Color Cortical Opacity PSC opacity	**No evidence of an association between H_2S exposure and LOCS score in any of the 4 outcome categories**		Age Smoking habits	Bates et al, 2017

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Ecological	1,635 subjects aged 18-65	2008-2010	Neuropathy evaluated through: Ankle Reflex Test Filsment Test Tuning Fork Bio-Thesiometer NCIS (Neuropathy Composite Index Score)	**No evidence of an association of any of the indicators of peripheral neuropathy with exposure to ambient H_2S over a period of 30 years.**	An average time-weighted H_2S exposure over the last 30 years was calculated for each participant. Concentrations surfaces were created using kriking. Range 0-58 ppb (median 11 ppb, average 13 ppb) 4 exposure categories defined Q1 (0-5.6 ppb); Q2 (5.6-10.6 ppb) Q3 (10.6-18.4 ppb): Q4 (18.4-57.9 ppb)	Age Ethnicity Education level Income	Pope et al, 2017
Time series	--	2006-2009	Excess risk (%) of increased dispensing of anti-asthma drugs (alla drugs and adrenergic drugs) Results given per 10 µg/m^3 pollutant increase	**H_2S** *24-h mean pollution (all drugs)* Lag (3-5) ER 2% (0.4-3.6) **PM_{10}** *24-h mean pollution (all drugs)* Lag (3-5) ER 0.9% (0.1-1.8) Lag (6-8) ER -1.3% (-2.1-(-0.5)) *24-h mean pollution (adrenergic drugs)* Lag (3-5) ER 1.3% (0.4-2.2) Lag (6-8) ER -1.7% (-2.6-(-0.8)) *1-h peak pollution (all drugs)* Lag (3-5) ER 0.3% (0.2-0.4) Lag (6-8) ER 0.1% (0.0-0.2) Lag (9-11) ER 0.1% (0.0-0.2) Lag (12-14) ER 0.1% (0.0-0.2) *1-h peak pollution (adrenergic drugs)* Lag (3-5) ER 0.3% (0.2-0.5) Lag (6-8) ER 0.1% (0.0-0.3) Lag (9-11) ER 0.1% (0.0-0.2)	Daily (midnight to midnight) 1-h peak pollution and daily 24-h mean concentrations. For each day authors calculated the three-day moving average from the daily mean and peak values of the same day, the day before and two day before (lag 0-2), 3 to 5 day before (lag 3-5), 6 to 8 day before (lag 6-8), 9-11 day before (lag 9-11) and 12.14 day before (lag 12-14)	Temperature Relative humidity Total pollen count Influenza epidemics Day-of week and holiday binary variables Time trend Season trend	Carlsen et al, 2012
Cross-sectional	181,558 subjects >18 year	2003-2009	Percentage increases in risk of death (IR%) for all natural cause (ICD-10 code A00-R99) following an interquartile range increase in pollutants. Analyses perfomred stratifying on season (winter/summer), gender and age (<80 years and ≥80)	**H_2S** *Un-stratified model* lag3 IR%=-1.54 (-3.00-(-0.05)) *Summer* lag1 IR%=5.05 (0.61-9.68) *Summer* lag2 IR%=5.09 (0.44-9.97) *Winter* lag3 IR%=-1.99 (-3.55-(-0.41)) *Males* lag0 IR%=2.26 (0.23-4.33) *≥80 years* lag0 IR%=1.94 (0.12-1.04) *≥80 years* lag1 IR%=1.99 (0.21-1.04) *<80 years* lag2 IR%=-2.87 (-5.38-(0.30)) **PM_{10}** *<80 years* lag0 IR%=2.81 (0.00-5.70)	A lag time of up to 4 days (five lags: 0–4) was introduced separately to the analyses. Lag definitions are as follows: lag 0: air pollution exposure on the same day as death occurred, lag 1–4: air pollution exposure 1 day before (lag 1) and up to 4 days before (lag 4) the death occurred. Pollutants: NO_2, PM_{10}, SO_2, H_2S, O_3	Each pollutant Temperature Relative humidity	Finnbjornsdottir et al, 2015

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ICELAND							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Population-based cohort	13,383 patients (≥18 years old) with a total of 32961 emergency hospital visits	2007-2014	**Heart diseases:** Ischemic heart diseases (I20-I27) Cardiac arrest (I46) Cardiac arrhythmias (I48) Heart failure (I50)	**Unstratified model**[a] Lag0 p-trend=0.0038 (+) Lag2 p-trend=0.0027 (+) Lag4 p-trend=0.0483 (-) **Gender stratification**[b] *Females* Lag0 p-trend=0.0000 (+) Lag2 p-trend=0.0004 (+) Lag4 p-trend=0.0010 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0000 (+) Lag2 p-trend=0.0000 (+) Lag3 p-trend=0.0000 (+)	Ambient air concentrations for NO_2, O_3, PM_{10}, SO_2 and H_2S in μg/m^3 Meteorological data: temperature, relative humidity, wind speed and wind direction. H_2s concentrations divided in five 10° sections (A-E) and the average 24-hour H_2S concentration in each section was calculated. Different exposure levels of H_2s were estimated by different percentiles: 50% 2.46 μg/m^3 60% 3.16 μg/m^3 70% 4.14 μg/m^3 80% 5.74 μg/m^3 85% 7.00 μg/m^3 90% 8.80 μg/m^3 95% 11.68 μg/m^3. Distance from main roads (>10.000 cars per day) in the Reykjavik capital area was calculated for each individual's residential street and divided into categories of traffic exposure zones and used as a surrogate for traffic related exposure. To estimate H_2S exposure in different sections of the Reykjavik capital area, a simple model was applied covering a 50° section from Hellisheidi power plant to the west, which includes the Reykjavik capital area.	[a]Gender, age group, season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature [b]Age group, season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature [c]Season, day of week, distance from Hellisheidi plant, traffic exposure zone, temperature	Finnbjornsdottir et al, 2016
			Respiratory diseases Acute lower respiratory infections (J20-J22) Chronic lower respiratory infections (J40-J46) Respiratory failure (J96)	**Un-stratified model**[a] Lag0 p-trend=0.0340 (-) **Gender stratification**[b] *Males* Lag0 p-trend=0.0003 (-) Lag2 p-trend=0.000 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0000 (-) Lag3 p-trend=0.0013 (-)			
			Stroke: Cerebrovascular disesases (I61-I69) other than subarachnoid haemorrhage (I60) and transient cerebral ischaemic attacks and related syndromes (G45) and vascular shyndromes of brain in cerebrovascular diseases (G46)	**Un-stratified model**[a] Lag0 p-trend=0.0038 (+) Lag1 p-trend=0.0086 (-) **Gender stratification**[b] *Males* Lag0 p-trend=0.0104 (+) Lag1 p-trend=0.0002 (-) **Age stratification**[c] Older (≥73 yr) Lag0 p-trend=0.0136 (+) Lag1 p-trend=0.0042 (-) *p-trend across the percentiles of H_2S concentrations;* *(+) positive dose-response association* *(-) negative dose-response association*			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	***Mortality*** Non-accidental mortality (0-999)	*Men+women* HR II *vs* I=0.82 (0.77-0.87); p<0.0001 HR III *vs* I=0.87 (0.79-0.96); p=0.006 HRlinear=0.94 (0.91-0.97); p<0.001 *Women* HR II *vs* I=0.76 (0.70–0.82); p<0.001 HR III *vs* I= 0.82 (0.71–0.94); p<0.001	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 μg/m^3 not-exposed; Group II: 5–20 μg/m^3 – low exposure; Group III: >20 μg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 μg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			All malignant neoplasms (140-239)	*Men+women* HR II *vs* I=0.83 (0.75-0.92); p<0.001 HR III *vs* I=0.79 (0.65-0.95); p=0.015 HRlinear=0.92 (0.87-0.97); p=0.009 *Women* HR II *vs* I=0.75 (0.63–0.89); p=0.001 HR III *vs* I=0.63 (0.45–0.83); p=0.003			
			Diseases of the circulatory system (390-419)	*Men* HR II *vs* I=0.84 (0.72–0.98); p=0.038			
			Ischemic heart disease (410-414)	*Men+women* HR III *vs* I=0.60 (0.41-0.88); p=0.011 HRlinear=0.85 (0.76-0.95); p=0.004 *Men* HR III *vs* I=0.49 (0.28–0.87); p=0.016			
			Acute myocardial infarction (410)	*Men+women* HR III *vs* I=0.45 (0.25-0.81); p=0.007 HRlinear 0.75 (0.63-0.89); p=0.001 *Men* HR III *vs* I=0.36 (0.15–0.86); p=0.018			
			Cerebrovascular diseases (430-438)	*Men+women* HR II *vs* I=0.74 (0.61-0.90); p=0.002 *Men* HR III *vs* I= 0.70 (0.51–0.96); p=0.025 *Women* HR II *vs* I=0.76 (0.59–0.97); p=0.036			
			Diseases of the respiratory system (460-519)	*Men+women* HRlinear 1.12 (1.00-1.25); p=0.040 *Women* HR II *vs* I=1.47 (1.00–2.15); p=0.046			
			Pneumonia (487)	*Men+women* HRlinear 1.27 (1.02-1.58); p=0.031			
			Hospitalization All malignant neoplasms (140-239)	*Men+women* HR III *vs* I=0.86 (0.75-0.98); p=0.034 HRlinear 0.95 (0.91-0.99); p=0.049			
			Malignant neoplasm of ovary and other uterine adnexa (183)	*Men+women* HRlinear 1.40 (1.07-1.84); p=0.014 *Women* HR II *vs* I=2.64 (1.40–4.98); p=0.003 HR III *vs* I=2.50 (1.00–6.25); p=0.049			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	Diseases of the nervous system and sense organs (320-389)	<u>*Men+women*</u> HR II *vs* I=1.13 (1.03-1.24); p=0.006 HRlinear 1.06 (1.01-1.11); p=0.003	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 μg/m^3 not-exposed; Group II: 5–20 μg/m^3 – low exposure; Group III: >20 μg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 μg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			Disorders of the peripheral nervous system (350-359)	<u>*Men+women*</u> HR II *vs* I=1.77 (1.42-2.21); p<0.001 HR III *vs* I=1.61 (1.13-2.30); p=0.008 HRlinear 1.22 (1.10-1.36); p<0.001 <u>*Men*</u> HR III *vs* I=1.66 (1.15–2.40); p=0.007 <u>*Women*</u> HR II *vs* I=1.83 (1.38–2.43); p<0.001 HR III *vs* I=1.81 (1.18–2.78); p=0.006			
			Diseases of the circulatory system (390-459)	<u>*Men+women*</u> HRlinear 1.04 (1.01-1.07); p=0.006			
			Heart failure (428)	<u>*Men+women*</u> HR III *vs* I=1.54 (1.26-1.94); p<0.001 HRlinear 1.14 (1.07-1.22); p<0.001 <u>*Men*</u> HR III *vs* I=1.42 (1.04–1.95); p=0.026 <u>*Women*</u> HR III *vs* I=1.65 (1.23–2.21); p=0.001			
			Cerebrovascular diseases (430-438)	<u>*Men+women*</u> HRlinear 0.93 (0.88-0.98); p=0.017 HR II *vs* I=0.87(0.79–0.96); p=0.015 HR III *vs* I=0.78 (0.65–0.94); p=0.008			
			Diseases of veins and lymphatics, and other diseases of circulatory system (451-459)	<u>*Men+women*</u> HR II *vs* I=1.46 (1.28-1.66); p<0.001 HRlinear 1.15 (1.08-1.22); p<0.001 <u>*Men*</u> HR II *vs* I=1.54 (1.28–1.86); p<0.001 <u>*Women*</u> HR II *vs* I=1.40 (1.17–1.68); p<0.001 HR III *vs* I=1.35 (1.02–1.80); p=0.035			
			Pneumonia (487)	<u>*Men+women*</u> HR II *vs* I=1.36 (1.18-1.57); p<0.0001 <u>*Men*</u> HR II *vs* I=1.35 (1.11–1.64); p=0.002<u>*Women*</u> HR II *vs* I=1.37 (1.10–1.71); p=0.005 HR III *vs* I=1.64 (1.18–2.28); p=0.003			
			Chronic obstructive pulmonary disease, and allied conditions (490-496)	<u>*Men+women*</u> HRlinear 1.14 (1.06-1.23); p<0.001 HR II *vs* I=1.30 (1.08-1.57); p=0.006 HR III *vs* I=1.98 (1.49-2.63); p<0.0001			

Table 2. Epidemiological studies based on proxy-individual level exposure metrics, by geographical area, evaluating health status of populations residing in geothermal areas considered. (*Continued*)

ITALY							
Study design	**Study sample**	**Study period**	**Outcome**	**Results (95%CI)**	**Exposure assessment**	**Confounders**	**Reference**
Residential-cohort	33,804 subjects (16,353 males and 17,451 females) residing in six municipalities of SGA, for a total of 391,002 person-years	1998-2016	Chronic obstructive pulmonary disease, and allied conditions (490-496)	*Men* HR III *vs* I=2.09 (1.45–3.02; p<0.0001 *Women* HR II *vs* I=1.44 (1.06–1.95); p=0.015 HR III *vs* I=1.84 (1.18–2.86); p=0.007	HR and 95%CI computed using H_2S metric as a categorical variable (Group I: <5 µg/m^3 not-exposed; Group II: 5–20 µg/m^3 – low exposure; Group III: >20 µg/m^3 – high exposure) or using the H_2S metric as a continuous variable, estimating the HRs associated to increases of 7 µg/m^3 of H_2S concentrations	Sex, socio-economic status, calendar period	Nuvolone et al, 2019
			Other diseases of the respiratory system (510-519)	*Men+women* HR II *vs* I=0.57 (0.49-0.66); p<0.0001 HR III *vs* I=0.59 (0.47-0.77); p<0.0001 HRlinear 0.77 (0.74-0.84); p<0.001 *Men* HR II *vs* I= 0.56 (0.47–0.66); p<0.0001 HR III *vs* I= 0.62 (0.47–0.82); p=0.003 *Women* HR II *vs* I= 0.55 (0.44–0.69); p<0.0001 HR III *vs* I=0.60 (0.41–0.88); p=0.009			

Notes – vs: versus; ppb: part per billion; NO_2: nitrogen dioxide; O_3: Ozone; PM_{10}: particulate matter with diameter <10 µm; SO_2: sulfur dioxide; H_2S: hydrogen sulfide; HR: Hazard Ratio.

***conflict of Interest Statement**

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
