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The Multi-Country Multi-City Collaborative Research Network

An international research consortium investigating environment, climate, and health

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Abstract: Research on the health risks of environmental factors and climate change requires epidemiological evidence on associated health risks at a global scale. Multi-center studies offer an excellent framework for this purpose, but they present various methodological and logistical problems. This contribution illustrates the experience of the Multi-Country Multi-City Collaborative Research Network, an international collaboration working on a global research program on the associations between environmental stressors, climate, and health in a multi-center setting. The article illustrates the collaborative scheme based on mutual contribution and data and method sharing, describes the collection of a huge multi-location database, summarizes published research findings and future plans, and discusses advantages and limitations. The Multi-Country Multi-City represents an example of a collaborative research framework that has greatly contributed to advance knowledge on the health impacts of climate change and other environmental factors and can be replicated to address other research questions across various research fields.

Keywords: Environmental epidemiology; Climate change; Temperature; Air pollution; Multi-city; Two-stage; Time series

A global perspective on environmental risks, climate change, and health

Climate change and environmental degradation are widely considered the biggest threats faced by humanity in the 21st century.[1,2] These phenomena have been linked to an increase in exposure to several environmental hazards, such as nonoptimal temperature, air pollution, wildfires, floods, and other extreme weather events.[3] Their health impacts vary across regions and populations due to differences in exposure levels and vulnerability, and proper assessments require epidemiological studies that can provide both global comparisons and reliable estimates of local impacts. This contribution illustrates the experience of the Multi-Country Multi-City (MCC) Network, an international collaboration that has performed important multi-location epidemiological analyses in this research area. This piece kickstarts an article collection featuring the latest contributions from the MCC Network on various research topics relevant to environmental health.

The Multi-Country Multi-City Network

The MCC Collaborative Research Network is an international consortium working on a global research program aiming to produce epidemiological evidence on associations between environmental stressors, climate, and health (http://mccstudy.lshtm.ac.uk/). The collaboration started informally in a meeting at the annual conference of the International Society for Environmental Epidemiology in Basel in 2013, and it has developed over the years through correspondence between the participants and additional meetings held at other scientific conferences. The MCC sets a collaborative framework for developing multicenter epidemiological assessments by collecting health and environmental data from different locations across countries. The foundations of the network define that each member

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The MCC Network has worked since 2014 on a purely collaborative basis and has not so far received direct funding for its activities.

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What this study adds

This is the first contribution that presents the Multi-Country Multi-City (MCC) Collaborative Research Network, detailing the origin and purpose of the collaboration and the research work undertaken so far. In addition to information on the data collection and the multi-location database gathered over the years, this contribution illustrates the study protocol and the mode of collaboration adopted by the MCC Network, based on a flexible framework that promotes data sharing and collective participation. The article also offers an overview of the publications by MCC on different research topics, as well as the methodological developments supporting these works. Finally, this article kickstarts an article collection, with a series of epidemiological works to be published in Environmental Epidemiology, featuring the latest contributions from the MCC Network on topical environmental research issues.

can use the MCC database under the premise that they contribute with data from a specific country.

The Multi-Country Multi-City database

Through this consortium, the MCC Network has gathered the largest epidemiological database ever assembled for studying the health effects of environmental factors, including information from hundreds of locations within dozens of countries. The main database consists of daily time series of environmental measurements, including various weather indices and pollution levels, mortality counts for all and specific causes, and location-specific meta-variables on climatological, socio-economic, demographic, and infrastructural characteristics. At the time of writing, the database includes datasets from 1150 locations in 54 countries in largely overlapping periods between 1969 and 2021, totaling over 200 million deaths. These data are complemented by a wide collection of environmental measures gathered from global reanalysis databases and remote-sensing instruments and linked to each site. The set of MCC locations covers a wide range of regions, populations, and climates, including high, middle, and low-income countries, and spans from arid and tropical areas to temperate and cold latitudes (Figure 1). The database is continuously updated by the MCC participants and complemented with data from additional countries/locations. An inventory of the available datasets is kept centrally and shared with all the participants.

Study protocol, data sharing, and mode of collaboration

The key feature of the MCC partnership is to provide researchers with opportunities for pursuing specific research questions at a global scale in a flexible collaborative framework. The method of collaboration is defined by a study protocol drafted at the beginning of the collaboration. Briefly, the work is organized around subproject proposals that can be submitted independently by any participant, who will then lead on analyses and publications. Each proposal states the objectives of the subproject and identifies the relevant data, and it is circulated among the participants responsible for each dataset, who can agree on its use and can contribute as coauthors. The protocol sets guidelines that limit the use of the data to agreed subprojects, outlines authorship rules, and prevents overlap between subprojects. This formal yet flexible mode of collaboration offers scientific independence in addressing a variety of research topics using a massive multi-country database while ensuring collective participation, control of the use of data, and consistency of designs and methods. The work is supervised and coordinated by the MCC Scientific Committee.

Activities within the MCC Network promote a collaborative environment based on data sharing. The participation in the consortium is conditional on the provision of original data in a format consistent with the MCC database, and the willingness to share them. Each participant retains the rights to their data and responsibility regarding their use, stipulated separately with the original data providers. The data-sharing agreement is limited to each subproject. While each participant allows others to use these data in their analyses, they have access to the full database and enjoy the benefits of collaborating in various subprojects and publications. To the extent possible, examples reproducing published results, including code, software, and subsets of data, are made available as Supplemental material; http://links.lww.com/EE/A299 and in publicly accessible repositories, thus increasing transparency and facilitating replication.

Methodological contributions

The availability of such a massive database allows standardized analyses of local/regional data based on state-of-the-art epidemiological designs and statistical methods. Indeed, the MCC Network has contributed to the development and application of a number of techniques for environmental epidemiological studies. These include first the use of time series regression analysis and distributed lag linear and nonlinear models to describe complex health associations with environmental stressors, the extension of two-stage designs and meta-analytical models to perform pooled analyses on multi-center data,[4,5] the use of self-matched designs with conditional regression models,[6–9] and sample size studies.[10] Further work within MCC has led to the development of analytical frameworks for climate change impact projections,[11] measures of attributable risks,[12] global reconstructions of air pollution exposures,[13] and detailed risk mapping.[14,15] More focused methodological contributions

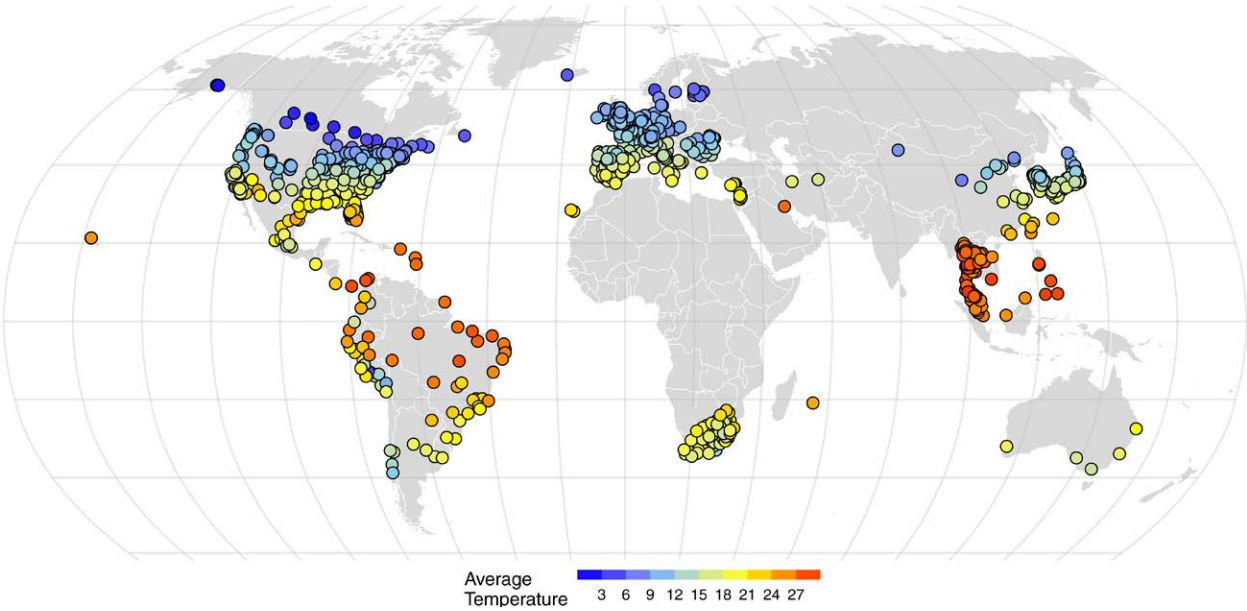

Figure 1. Map of current MCC locations.

have focused on the definition of heatwaves,[16] heat stress, and temperature variability indices,[17] the analysis of temporal and geographical variation in risks,[18] interactive effects,[19] the identification and analysis of minimum mortality temperature,[20] seasonal patterns,[21,22] and the use of data reanalysis for epidemiological studies.[23–25]

Research topics, published work, and future directions

The MCC Network has already contributed key evidence on the associations between various environmental stressors, climate, and health (Figure 2). The extensive evidence has been presented through peer-reviewed publications in leading environmental, epidemiological, and medical journals, and contributions in thematic conferences. The works published so far are summarized below by research topic, with individual articles listed in eTable 1 in the Supplementary Material (Appendix; http://links.lww.com/EE/A299).

Temperature-related risks

The MCC Network kickstarted its work with two seminal publications presenting a multi-country analysis of the health risks of nonoptimal temperature and the associated excess mortality due to heat and cold.[26,27] These contributions provided novel results on the relative magnitude of cold- and heat-related impacts and the importance of nonextreme nonoptimal temperatures. The following works investigated other aspects, such as mortality risks associated with heat waves,[28] long-term impacts and mortality displacement,[29] effects of hot nights,[30] the role of temperature in seasonal mortality,[31] and the geographical variation of the minimum mortality temperature.[32] Other analyses focused on temperature-related risks on cause-specific mortality outcomes, such as various cardiovascular endpoints,[33] stroke,[34] and suicides.[35,36] A series of articles presented evidence of associations with alternative indices, such as inter- and intra-day temperature change.[37–40] More recent studies applied design extensions to comprehensively map mortality risks associated with heat and cold across European cities or the whole globe.[14,15] Similar methods were also used to reconstruct the global impacts of heat waves,[41] cold spells,[42] and temperature variability.[43] Finally, other works evaluated the health effects using different heat stress metrics,[17] and compared estimates using weather station and climate reanalysis data.[23,24]

Assessment of vulnerability to nonoptimal temperature

In a related line of research, the MCC researchers have tried to characterize differences in vulnerability across geographical areas and populations. Two initial studies assessed long-term variations and changes in susceptibility across the summer in heat-mortality risks, respectively.[18,44] A following study then assessed changes across cities related to various urban characteristics.[45] Other analyses focused on effect modification by environmental factors, such as humidity,[46] air pollution,[47] and greenness.[48] More recent studies examined the role of temperature fluctuation and frequency on heat-mortality associations.[49,50]

Short-term effects of air pollution

A second phase of the work of the MCC Network extended the scope of the research beyond temperature-related risks, in particular assessing the short-term effects of air pollution in multi-country analyses. Influential works presented evidence on mortality risks associated with various pollutants, specifically particulate matter,[51,52] nitrogen dioxide,[53] ozone,[54] carbon monoxide,[55] and sulfur dioxide.[56] The following works tried to differentiate risks depending on particulate composition,[57] and explore interactive effects between pollutants and heat, respectively.[19,58] Another study examined the lagged effects of air pollution on acute kidney injury.[59] Finally, a recent article compared risk estimates obtained using observed and modeled air pollution measures.[25]

Health impacts of climate change

Another important part of the work of the MCC consortium has focused on climate change and the projection of health impacts in scenario-based assessments. A first set of studies provided projections of excess mortality due to heat and cold under various pathways of greenhouse gas emissions and global temperature thresholds consistent with the Paris Agreement, respectively.[60,61] Other studies quantified the future impacts of heat waves and diurnal temperature range,[62,63] examined potential adaptive mechanisms to cold and heat in a changing climate,[64] and assessed the role of population aging.[65] A pivotal work of MCC quantified the burden of heat-related mortality attributable to recent human-induced climate change.[66] Two studies projected potential future changes in seasonal mortality and excess deaths due to short-term exposure to ozone, respectively.[67,68] Finally, other analyses predicted global health burdens

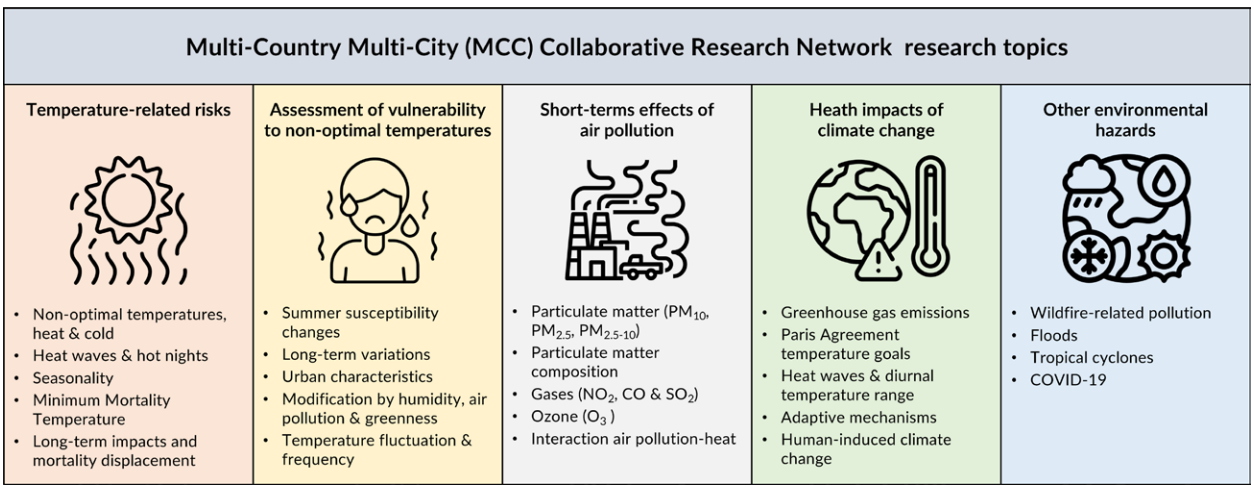

Figure 2. Main research areas and topics investigated by the MCC Network.

induced by temperature increases,[69] and performed probabilistic estimates of impacts in future summer seasons.[70]

Other environmental hazards

More recently, the work of the MCC network has extended to the global analysis of other environmental hazards and health endpoints. Specifically, the modeling framework has been adapted to examine the mortality risks associated with wildfire-related pollution,[71] floods,[72] and tropical cyclones.[73,74] Another study instead assessed the role of environmental factors on the incidence of COVID-19.[75]

Current and planned work will significantly extend the research scope of MCC. First, there is an ongoing process to update and extend data collection on cause-specific mortality outcomes, as well as morbidity records, primarily hospital admissions and birth outcomes, to replicate analyses on other health associations. In addition, the modeling framework is currently being applied to examine health risks associated with other environmental factors, such as desert dust, airborne pollen, and rainfall. Planned analyses are meant to offer a better characterization of health risks across populations, identifying drivers of vulnerability, as well as detecting health-relevant air pollution components and weather stress indices. An important line of research is to improve projections of health impacts under climate change scenarios and to identify effective adaptation pathways. This work will be complemented by specific methodological extensions that will improve the existing design and modeling framework.

Important aspects

The MCC study presents several advantages if compared to previous epidemiological investigations on the same topic area. First, its multi-country multi-center framework offers a dual local/global perspective that is critical in planetary health and climate change research. The analytical scheme involves the application of consistent analytical procedures to estimate associations across hundreds of locations characterized by various climates, diverse demographic and socio-economic features, and different levels of development and infrastructure. This two-stage design preserves the possibility of inspecting interesting local features, while at the same time allowing global comparisons of environmental impacts across areas of the world. Most of the previous studies on the same research subject were limited to specific cities or regions with relatively homogeneous populations,[76–78] or included a few locations across several areas, with issues of representativeness and insufficient statistical power to inspect more subtle effects.[79] While the coverage of the MCC database is incomplete, with entire areas of the world such as most parts of Africa and the Middle East that are not represented (see Figure 1), the scope of the study is truly global, and recent extensions have allowed comprehensive risk mapping through extrapolation techniques.[14,15]

Another important advantage of the MCC network is its mode of collaboration, inspired by principles of openness and data sharing. This has contributed to the collection and freedom of use of the massive database described above while preserving control over the use of the data provided by each participant. This approach can be adopted more broadly in climate change research and more generally in environmental health research to perform global epidemiological analyses on various risk factors. However, it must be acknowledged that the use of data other than aggregated time series can present more severe confidentiality issues, which must be accounted for and can pose limitations to this collaborative scheme.

Finally, the MCC Study benefits from a flexible protocol of work that maximizes research independence within a collaborative environment. The focus on subproject proposals independently submitted by each participant allows more freedom when compared to rigid research schedules discussed collectively and prespecified at the beginning of the study. However, it should be acknowledged that this mode of collaboration has also some limitations, such as the absence of a coherent plan with a linked set of research hypotheses to be addressed during the course of the study, and difficulties in ensuring consistent methodological approaches across subprojects.

Conclusions

The MCC Network has provided an important contribution to research on the health risks associated with environmental hazards, and to understand and quantify the health impacts of climate change. Past, ongoing, and planned activities within the MCC Network form a program of research that explores key aspects of environment and climate-health associations, and it has already provided original evidence that significantly extends our knowledge on the topic. In particular, the collaborative scheme and study designs proposed by the MCC network offer a way to perform epidemiological investigations at a global scale, while at the same time illustrating geographical and temporal differences across populations and areas determined by local characteristics. This duality is vitally important in climate change research, where global policies to mitigate global warming and its health risks must be implemented through and complemented with local-scale initiatives, legislations, and interventions, which account for area-level differences in projected impacts, resilience potential, and resources.

This contribution is an introductory piece of an article collection that will be published in Environmental Epidemiology in the next weeks, featuring the latest works by MCC on topical environmental research issues. The multi-center collaborative framework adopted by the MCC Network, based on mutual contribution and data sharing, will be hopefully reproduced and extended more broadly for addressing other environment-related issues and for extending the research capability in this area.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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