https://jrhm.org/

Journal of
Reproductive Healthcare
and Medicine

Indian Society for the Study of Reproduction & Fertility

Commentary

Reproductomics: An impending driver for exposome research

Pradyumna Kumar Mishra[1], Roshani Kumari[1], Ruchita Shandilya[1], Pooja Ratre[1], Arpit Bhargava[1], Neelam Pathak[2], Nirmal Kumar Lohiya[3]

[1]Department of Molecular Biology, ICMR-National Institute for Research in Environmental Health, Bhopal, Madhya Pradesh, [2]Palace Orchard Resident's Society, Bhopal, Madhya Pradesh, [3]Department of Zoology, Centre for Advanced Studies, University of Rajasthan, Jaipur, Rajasthan, India.

***Corresponding author:**
Pradyumna Kumar Mishra, Department of Molecular Biology, ICMR-National Institute for Research in Environmental Health, Bhopal, Madhya Pradesh, India.

pkm_8bh@yahoo.co.uk

Received : 05 September 2022
Accepted : 07 November 2022
Published : 10 December 2022

DOI
10.25259/JRHM_16_2022

Quick Response Code:

ABSTRACT

In our quest to recognize the role of extrinsic and intrinsic environmental factors that can profoundly affect human health, the exposome paradigm proffers an exciting avenue of research. Continuous human biomonitoring would be unfeasible because the exposome is longitudinal and dynamic. Therefore, the reproductive life course of exposome should be put together from cross-sectional snapshots at critical periods such as *in utero*, early childhood, adolescence, and adulthood. Of course, over the following decades, the exposome paradigm will continue to evolve in terms of its conceptual and methodologic framework. Still, our overarching goal should be to delineate underlying molecular mechanisms that promote health while preventing disease at the population level.

Keywords: Environmental health, Human biomonitoring, Exposomics, Biomarkers, Molecular reproduction, Translational research

Reproduction might be biology's most complex riddle. Nevertheless, the purpose is simple as it favors genetic diversity. This assortment enhances the fitness of the upcoming phenotypes by recreating resistant genotypes that are evolutionary and more adaptable. Extending from American geneticist Hermann Joseph Muller's truly unifying explanation; it would perhaps not be erroneous to assume that meiotic recombination results in maximum genetic diversity by entirely using possible gene mutations.[1] Initially, Muller's postulate seemed elegant, but evidence from several molecular epidemiological studies garnered later caused ambiguity. In the post-genomics era, careful examination using omics-based approaches revealed that humans have a shockingly high mutation rate. Each of us is born with approximately *de novo* 70 genetic errors that our parents did not have. Conventionally, mutations are believed to lessen an organism's fitness. Therefore, this important revelation about the accumulation of mutations resulting from meiotic cross-over and recombination posed more of a puzzle than reproductive biologists primarily thought. However, the quick realization that humans did not go extinct in the evolutionary course indicated the possible existence of less understood mechanisms of taking out unfavorable genetic garbage.[2] With the advent of more efficient, accurate, and high throughput genome sequence technologies, the precise estimate for a fraction of the genome, that is, "functional" was found to be about 10% (only). Aligning with this view, if natural selection is believed to act on each mutation independently, the resulting error load and loss in average fitness contradict the subsistence of humanity. Although it is largely agreed that the natural selection process

might prevent the unlimited accumulation of deleterious mutations, retrospective analysis of multiple birth cohort studies over the decades offers a contrasting perspective. Say, for instance, exposures to environmental toxins have a profound, life-long, and sustained impact on human health, which begins from conception. Exposure to various physical, chemical, or biological factors during pregnancy perturbs the fetal genomic and epigenomic machinery.[3,4] Given the numerous unique methodological challenges, establishing a linear association between human reproduction and the adverse selection of genetic errors is an ambitious task. Aberration in the genomic and epigenomic landscape is conjectured to be exceedingly pertinent to the evolutionary discourse, as it occupies a substantive account in the complex interplay of the genotype-phenotype relationship[5] Although molecular biologists understand a few challenges in these methodologies, multi-scale missing links exist in the critical windows of vulnerability from stages of conception to death.[6] Hence, the challenges are enormous, but cutting-edge technological advancements may help us set priorities for this newly evolving fascinating field of "reproductomics."

The "exposome" is an emerging field of science. The term was invented in 2005 by cancer epidemiologist Dr. Christopher P. Wild. Briefly, exposome refers to the totality of exposures a human experiences over a lifetime and the cumulative impact of those exposures on the body. Included in the mixture of vulnerabilities is the billions of naturally occurring and manufactured chemicals such as heavy metals and persistent organic pollutants; physical agents that include noise, vibration, and temperature; macro-level factors including population density and sanitation; and a spectrum of lifestyle factors such as diet, physical activity, stress, and sleep. The evaluation of cumulative risks for any given biological endpoint (as infertility, in this case) will include analysis, characterization, and possible quantification of the combined threats from multiple environmental stressors.[7-9] Let us try to help understand this with the help of an example. Suppose for a hypothesis-driven study, the absolute measure of a chemical risk associated with either male or female infertility factor must be determined. Once a pollutant traverses our body, it either gets accumulated or is processed metabolically and subsequently excreted. For real-time human monitoring, it could be the dose/concentration of the parent compound, its metabolite, or conjugated derivative with endogenous molecules through enzymatically catalyzed transformations which can be studied using analytical cutting-edge tools and techniques.[10-12]

On the other hand, for understanding the exposure's molecular repercussion, the mainstay of research will have to be a combinatorial "omics-based approach" involving biomolecules such as DNA, RNA, proteins, and metabolites. Large-scale screening of genes coding for proteins, regulatory elements, and non-coding sequences (genomics), RNA and gene expression (transcriptomics), protein expression (proteomics), metabolites, and metabolic pathways (metabolomics) will help the identification of essential genes, trails, and protein expression signatures in the suitable biological matrix of sizeable cohorts of men and women. Well, gametogenesis is a highly intricate physiological process; therefore, the outcome of such targeted strategies needs to be replicated in more than one cohort to infer the dose-response relationships.[13-15]

Given the numerous unique methodological challenges, understanding the molecular associations between gene-environmental interactions and human reproduction and development are an ambitious goal. Aberration in the epigenomic landscape is conjectured to be exceedingly pertinent to reproductive health, as it occupies a substantive account in the complex interplay of the genotype-phenotype relationship.[16] Although molecular biologists understand a few challenges in these methodologies, multi-scale missing links exist in the critical windows of vulnerability from conception to 37–40 weeks of gestation.[17] Novel methodologies for confronting these challenges are the need of the hour if we aim to understand better the inadequacies that currently characterize human reproduction intending to improve population health.

Beyond doubt, the concept of exposome is an emerging paradigm that encompasses all environmental exposures from conception onward. It offers significant promise toward understanding the subtle and elegant modulation of fidelity of transmissible non-heritable characteristics and complex non-Mendelian disease traits. This novel paradigm not only computes the totality of non-genetic exposures from preconception through sensitive windows but also recognizes associated patterns of adverse outcomes and impairments later in childhood or adulthood.[18,19] In a much broader sense, the evaluation of exposome-reproductive health relationships is not only restricted to windows of vulnerability but also extends well beyond and involves three overlapping domains:

1. External environmental factors include rural, semi-urban, urban environments, and climatic conditions.
2. Dietary factors include physical activity, habits, infection, and occupation.
3. Internal environment biological factors include metabolites, gut microbiome, oxygen-radical injury, sub-clinical inflammation, depression, anxiety, and stress.

Of late, four large-scale research initiatives have been launched: (i) The Human Early-Life Exposome (HELIX) project, which seeks to define the pregnancy and early life exposomes and health; (ii) The EXPOsOMICS project, which has a conceptual framework of a life-course approach to a broader range of exposures.[20,21] Whereas the former (HELIX), funded through the European Commission's FP7

Exposome Programme, focuses on the early-life exposome of six prospective birth cohort studies and aims to merge all environmental exposures that mothers and their respective children are exposed to and link this to the health, growth, and development of children; the latter (EXPOsOMICS) is a collaborative project funded through the European Commission's FP7 Exposome Programme focuses explicitly on air pollution and water contaminants, and to link these exposures to biochemical and molecular changes in the body. In addition, (iii) the Health and Environment-wide Associations based on Large population Surveys (HEALS) supported by the Framework Programme of the European Commission. The HEALS approach combines and categorizes environmental, socioeconomic, exposure, biomarker, and health effect data and includes all the procedures and computational sequences necessary for applying bioinformatics coupling, thus effective data mining and biological and exposure modeling to guarantee that environmental exposure-health associations are studied comprehensively. Unlike the three EU-funded projects, (iv) the Health and Exposome Research Center (HERCULES) cohort, a project that is being supported and supervised by the National Institute of Environmental Health Sciences, USA under their Environmental Health Sciences P30 Core Centers funding mechanism, which is a collaborative effort between researchers at Emory University and Georgia Institute of Technology.[22] The fundamental objective of setting up this center was to provide critical infrastructure and expertise to design and develop novel tools and technologies to generate exposure data, improve metabolomics approaches, and synthesize data into comprehensive computational models. These projects highlight two complementary strategies to characterize the exposome. First is the bottom-up approach, wherein the sources of acute exogenous exposures are identified, and the level of environmental exposure is measured in air, water, soil, or food. Second, in the top-down approach, the circulating levels of parent compounds and their metabolites and by-products are examined in biological matrices such as saliva, blood, urine, stool, semen, or other tissues.[23]

In recent years, two paradigms have been presented to facilitate how early environmental exposures might impact reproductive health, affecting health and disease across the lifespan, and, possibly, future generations.[24] The two paradigms are testicular dysgenesis syndrome (TDS) and ovarian dysgenesis syndrome (ODS). TDS refers to exposures that trigger regular testicular and genital development disruption, which manifests as genital-urinary malformations (e.g., hypospadias, cryptorchidism, Leydig cell dysfunction, astheno-necro-teratozoospermia, and testicular cancer). Correspondingly, the ODS posits that significant alterations in ovarian development and function cumulating from exposures during early development may influence folliculogenesis and steroidogenesis, ensuing in a gamut of undesirable reproductive outcomes that include polycystic ovarian syndrome, premature ovarian insufficiency or failure, alterations in menstruation, ovulation or time-to-pregnancy, pregnancy loss, and female reproductive tract cancers. The development of the subsequent generation(s) with a transgenerational inheritance pattern may be significantly impacted by the implications on the exposome, according to animal research conducted over the past few decades. Human evidence is more difficult to find, because demographic analysis of data spanning multiple generations will be necessary to establish a direct relationship. It is also true that the laboratory data in this field are hardly exhaustive, with most of the conclusions coming from research that only looked at a single diseased condition or reproductive ailment. During the past one and half decades, our molecular surveillance studies and systematic laboratory investigations comprehensively demonstrated that the risk of developing an environmental associated aberrant phenotype following pro-oxidant exposures involves a complex interplay of genomic and epigenetic reprogramming profoundly orchestrated by mitochondrial redox signaling.[25,26] Given that mitochondrial retrograde signaling-induced epigenomic impact is linked to neoplasticity, we adopted a cutting-edge tailored approach that is fundamental to drive these strategies from bench to bedside.[27,28]

The dynamic interface between the atmosphere, hydrosphere, cryosphere, and biosphere usually affects the climate and weather patterns at the Earth's surface.[29] The increasing accumulation of greenhouse gases from anthropogenic activities and growing regional concentrations of aerosol particulates are the two most significant drivers of observed climate change since the industrial revolution around 1750. The concentrations of greenhouse gases in the atmosphere which is being directly affected by anthropogenic activities are methane, carbon dioxide, nitrous oxide, ozone, and synthetic gases, such as chlorofluorocarbons and hydro-fluorocarbons.[30] Besides human activities, agricultural practices are also contributing to a significant share of the greenhouse gas emissions that are causing climate change. Whereas agricultural and livestock activities contribute to more than 17% of emissions, an additional 7–14% comes from changes in land use.[31] Nitrous oxide emissions from soils, fertilizer usage, dejections from grazing animals, and methane production by ruminants and rice cultivation are significant sources of greenhouse emissions.[32] Agriculture is expected to stay the foremost source of these non-carbon dioxide gases in the coming decades, which accounts for 58% of total anthropogenic nitrous oxide emissions and 47% of total anthropogenic methane emissions.[33] On the flip side, climate change has emerged as a significant threat to agriculture, food security, and millions of livestock populations worldwide. Although global human population growth has slowed as a whole, according to United Nations, the human population is likely to increase from 7.2 to 9.6

billion by 2050 as some developing nations are still growingly rapidly. India is likely to become the world's highest populated country, passing China around 2028.[34] This trend is particularly concerning as available agricultural technologies will not be able to match the needs of the incremental population growth. We shall be consuming more than we can produce, which might lead to a significant decline in food stock. This increase in population growth is driving the depletion of agricultural land for human settlement reducing agricultural and livestock production. Rich agricultural fields are affected by urbanization. Pressures of human settlement have destroyed forests leading to climatic changes, such as prolonged droughts and desertification.[35] Undoubtedly, we have started realizing that changes in climatic conditions will impede agricultural and livestock productivity. Rising temperatures; irregular rainfall patterns; frequent episodes of floods; and droughts are already influencing agricultural and livestock production. The day is not far when humanity will not only surpass a genuinely sustainable natural world but also shall reach a point where our food consumption limits shall overtake available resources that Earth could produce despite our technological capabilities.[36]

It is pivotal for us to realize that to match the unprecedented population growth, world food production is required to rise by 70%. Significantly, the rate of food production in the developing world (including India) will need to double; however, this projected augmentation in food production will have to overcome mounting energy prices, reduction of underground aquifers, systematic loss of farmland to urbanization, and frequent drought and flooding resulting from climate change.[37] The pace of agricultural and livestock production will have to increase at the same time when we are trying to slash global greenhouse gas emissions.[38] As we have already stated above that the production and distribution of food have been a significant contributors to greenhouse gas emissions, and thermal stress has surfaced as the most critical factor which would hamper livestock productivity in this changing climatic scenario.[39] In short episodes of heat stress, the livestock population may well acclimatize through a physiological response, but in the long term, adaptation in genetic and epigenetic trajectories might occur, resulting in giving rise to novel phenotypic diversity. Once the temperature crosses the threshold-neutral zone, living beings will be compelled to employ a portion of the energy to pledge thermal balance.[40] These undesirable stress conditions will significantly reduce the feed intake, growth performance, milk yielding capacity, sweating rate, panting, rectal temperature, respiratory rate, and water intake in livestock across the globe. The combinatorial effect of temperature and humidity will significantly affect not only the quality of life of the livestock population but also animal production and reproduction.[41] In males specifically, increased testicular temperature will result in low sperm output, reduced sperm motility, and a higher frequency of morphologically abnormal spermatozoa in the ejaculate. Furthermore, this thermal stress will reduce fertility, libido, and testicular degeneration. Whereas in females, the impact will not only impact the significant components of the reproductive system that includes (i) the estrus frequency; (ii) oocyte, granulosa, and theca cell numbers within the preovulatory follicle; (iii) developing embryo during early stages of development; (iv) corpus luteum and uterine endometrium; but would increase the loss of embryo and calving rates.[42,43] This year (2022), we have observed an unprecedented global heat wave (an increase of 1.1°C in temperatures above pre-industrial levels) that shattered records in nearly every corner of the planet. We are beginning to see widespread droughts in the Middle East; desertification in China and Africa; more intense hurricanes and storms reaching America; extensive melting of Arctic Sea ice and Greenland glaciers; more severe and extensive forest fires in Australia; and increasing ocean temperatures and shrinking of monsoon season in our own country India.[44] Here, we must highlight that these events are not disconnected but intertwined. The reality is that the impacts of climate change are here, and we are observing the unstoppable climatic catastrophes right now. As we foresee, we are on the brink of disaster. Although the "Paris climate agreement," signed on April 22, 2016, by 195 countries of the total 196 members of the United Nations, was considered a milestone toward addressing the climate and environmental challenges, it is now realized as an insufficient movement.[45] Nevertheless, provided the scientific knowledge and unbelievable technological abilities that we have today, the authors are pretty sure that we shall be able to avoid this global ecological collapse and continue to evolve and adapt with time.

Given the intricate relations between fecundity, gravid health, and later onset of disease phenotypes with the narrow and interlinked susceptible windows that portray the uncertain nature of human reproduction and development, molecular epidemiological studies would be uniquely suited for proof-of-concept exposome research in reproductive health. Such investigations will require the involvement of specialists from a wide range of disciplines (molecular biology, exposure sciences, epidemiology, statistics, and clinicians) and a multi-scale analysis single statistical approach, not independently as it is classically done. Analyzing these associations between the exposome and health will also require many exposure cohorts to be simultaneously included. It should not allow selective reporting of the associations within a specific population subset but provides a comprehensive outcome of both external and internal environmental risk factors.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

RK, PR and AB are thankful to the Indian Council of Medical Research (ICMR), Department of Health Research (DHR), Ministry of Health & Family Welfare, Government of India, New Delhi for providing fellowship support (RK, PR - SRF; AB - Post Doctoral Fellowship).

Conflicts of interest

Prof. Nirmal Kumar Lohiya is the Editor-in-chief of the journal. Pradyumna Kumar Mishra is one of the Editorial Board member of the journal.

REFERENCES

1. Shukla A, Bunkar N, Kumar R, Bhargava A, Tiwari R, Chaudhury K, *et al*. Air pollution associated epigenetic modifications: Transgenerational inheritance and underlying molecular mechanisms. Sci Total Environ 2019;656:760-77.
2. Mishra PK, Kumari R, Bhargava A, Bunkar N, Chauhan P, Tiwari R, *et al*. Prenatal exposure to environmental pro-oxidants induces mitochondria-mediated epigenetic changes: A cross-sectional pilot study. Environ Sci Pollut Res Int 2022;29:74133-49.
3. Mishra PK, Bunkar N, Raghuram GV, Khare NK, Pathak N, Bhargava A. Epigenetic dimension of oxygen radical injury in spermatogonial epithelial cells. Reprod Toxicol 2015;52:40-56.
4. Raghuram GV, Mishra PK. Stress induced premature senescence: A new culprit in ovarian tumorigenesis? Indian J Med Res 2014;140(Suppl 1):S120-9.
5. Bunkar N, Bhargava A, Khare NK, Mishra PK. Mitochondrial anomalies: Driver to age associated degenerative human ailments. Front Biosci 2016;21:769-93.
6. Bunkar N, Bhargava A, Chaudhury K, Sharma RS, Lohiya NK, Mishra PK, *et al*. Nucleic acids in maternal plasma: From biology to clinical translation. Front Biosci 2018;23:397-431.
7. Bhargava A, Pathak N, Sharma RS, Lohiya NK, Mishra PK. Environmental impact on reproductive health: Can biomarkers offer any help? J Reprod Infertil 2017;18:336-40.
8. Bhargava A, Tamrakar S, Aglawe A, Lad H, Srivastava RK, Mishra DK, *et al*. Ultrafine particulate matter impairs mitochondrial redox homeostasis and activates phosphatidylinositol 3-kinase mediated DNA damage responses in lymphocytes. Environ Pollut 2018;234:406-19.
9. Bhargava A, Shukla A, Bunkar N, Shandilya R, Lodhi L, Kumari R, *et al*. Exposure to ultrafine particulate matter induces NF-κβ mediated epigenetic modifications. Environ Pollut 2019;252(Pt A):39-50.
10. Mishra PK, Raghuram GV, Bhargava A, Pathak N. Translation research in molecular disease diagnosis: Bridging gap from laboratory to practice. J Glob Infect Dis 2011;3:205-6.
11. Shandilya R, Pathak N, Lohiya NK, Sharma RS, Mishra PK. Nanotechnology in reproductive medicine: Opportunities for clinical translation. Clin Exp Reprod Med 2020;47:245-62.
12. Mishra PK, Shandilya R. Nanophotonic biosensors as point-of-care tools for preventive health interventions. Nanomedicine 2020;15:1541-4.
13. Van Dijke I, van El CG, Lakeman P, Goddijn M, Rigter T, Cornel MC, *et al*. Dynamics of reproductive genetic technologies: Perspectives of professional stakeholders. PLoS One 2022;17:e0269719.
14. Karr TL. Reproductive proteomics comes of age. Mol Cell Proteomics 2019;18(Suppl 1):S1-5.
15. Bracewell-Milnes T, Saso S, Abdalla H, Nikolau D, Norman-Taylor J, Johnson M, *et al*. Metabolomics as a tool to identify biomarkers to predict and improve outcomes in reproductive medicine: A systematic review. Hum Reprod Update 2017;23:723-36.
16. Rasmussen L, Knorr S, Antoniussen CS, Bruun JM, Ovesen PG, Fuglsang J, *et al*. The impact of lifestyle, diet and physical activity on epigenetic changes in the offspring-A systematic review. Nutrients 2021;13:2821.
17. Santos S, Maitre L, Warembourg C, Agier L, Richiardi L, Basagaña X, *et al*. Applying the exposome concept in birth cohort research: A review of statistical approaches. Eur J Epidemiol 2020;35:193-204.
18. Vineis P, Robinson O, Chadeau-Hyam M, Dehghan A, Mudway I, Dagnino S. What is new in the exposome? Environ Int 2020;143:105887.
19. Vrijheid M, Basagaña X, Gonzalez JR, Jaddoe VW, Jensen G, Keun HC, *et al*. Advancing tools for human early lifecourse exposome research and translation (ATHLETE): Project overview. Environ Epidemiol 2021;5:e166.
20. Maitre L, Julvez J, López-Vicente M, Warembourg C, Tamayo-Uria I, Philippat C, *et al*. Early-life environmental exposure determinants of child behavior in Europe: A longitudinal, population-based study. Environ Int 2021;153:106523.
21. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, *et al*. The exposome in practice: Design of the EXPOsOMICS project. Int J Hyg Environ Health 2017;220(2 Pt A):142-51.
22. He L, Bulanova D, Oikkonen J, Häkkinen A, Zhang K, Zheng S, *et al*. Network-guided identification of cancer-selective combinatorial therapies in ovarian cancer. Brief Bioinform 2021;22:272.
23. Sobus JR, Tan YM, Pleil JD, Sheldon LS. A biomonitoring framework to support exposure and risk assessments. Sci Total Environ 2011;409:4875-84.
24. Quilaqueo N, Villegas JV. Endocrine disruptor chemicals. A review of their effects on male reproduction and antioxidants as a strategy to counter it. Andrologia 2022;54:14302.
25. Raghuram GV, Pathak N, Jain D, Pandey H, Panwar H, Jain SK, *et al*. Molecular characterization of isocyanate-induced male germ-line genomic instability. J Environ Pathol Toxicol Oncol 2010;29:213-34.
26. Raghuram GV, Pathak N, Jain D, Panwar H, Pandey H, Jain SK, *et al*. Molecular mechanisms of isocyanate induced oncogenic transformation in ovarian epithelial cells. Reprod Toxicol 2010;30:377-86.
27. Mishra PK, Bunkar N, Singh RD, Kumar R, Gupta PK, Tiwari RR, *et al*. Comparative profiling of epigenetic modifications among individuals living in different high and low air pollution zones: A pilot study from India. Environ Adv 2021;4:100052.
28. Mishra PK, Bhargava A, Kumari R, Bunkar N, Chauhan P, Mukherjee S, *et al*. Integrated mitoepigenetic signalling mechanisms associated with airborne particulate matter

exposure: A cross-sectional pilot study. Atmospheric Pollut Res 2022;13:101399.
29. Yao T, Wu F, Ding L, Sun J, Zhu L, Piao S, *et al*. Multispherical interactions and their effects on the Tibetan Plateau's earth system: A review of the recent researches. Natl Sci Rev 2015;2:468-88.
30. Zheng J, Chong ZR, Qureshi MF, Linga P. Carbon dioxide sequestration via gas hydrates: A potential pathway toward decarbonization. Energ Fuel 2020;34:10529-46.
31. Montzka SA, Dlugokencky EJ, Butler JH. Non-CO_2 greenhouse gases and climate change. Nature 2011;476:43-50.
32. Panchasara H, Samrat NH, Islam N. Greenhouse gas emissions trends and mitigation measures in Australian agriculture sector-a review. Agriculture 2021;11:85.
33. Lawrence NC, Tenesaca CG, VanLoocke A, Hall SJ. Nitrous oxide emissions from agricultural soils challenge climate sustainability in the US Corn Belt. Proc Natl Acad Sci USA 2021;118:e2112108118.
34. Ali S, Liu Y, Ishaq M, Shah T, Abdullah, Ilyas A, *et al*. Climate change and its impact on the yield of major food crops: Evidence from Pakistan. Foods 2017;6:39.
35. Satterthwaite D, McGranahan G, Tacoli C. Urbanization and its implications for food and farming. Philos Trans R Soc Lond B Biol Sci 2010;365:2809-20.
36. Kang MS, Banga SS. Global agriculture and climate change. J Crop Improv 2013;27:667-92.
37. An C, Sun C, Li N, Huang B, Jiang J, Shen Y, *et al*. Nanomaterials and nanotechnology for the delivery of agrochemicals: Strategies towards sustainable agriculture. J Nanobiotechnology 2022;20:11.
38. Zhang L, Tian H, Shi H, Pan S, Chang J, Dangal SR, *et al*. A 130-year global inventory of methane emissions from livestock: Trends, patterns, and drivers. Glob Chang Biol 2022;28:5142-58.
39. Collier RJ, Baumgard LH, Zimbelman RB, Xiao Y. Heat stress: Physiology of acclimation and adaptation. Anim Front 2018;9:12-19.
40. Boni R. Heat stress, a serious threat to reproductive function in animals and humans. Mol Reprod Dev 2019;86:1307-23.
41. Sammad A, Hu L, Luo H, Abbas Z, Umer S, Zhao S, *et al*. Investigation of metabolome underlying the biological mechanisms of acute heat stressed granulosa cells. Int J Mol Sci 2022;23:2146.
42. Durairajanayagam D. Lifestyle causes of male infertility. Arab J Urol 2018;16:10-20.
43. Findlay JK, Holland MK, Wong BB. Reproductive science and the future of the planet. Reproduction 2019;158:R91-6.
44. Azhar SS, Chenoli SN, Samah AA, Kim SJ, Murukesh N. The mechanism linking the variability of the Antarctic sea ice extent in the Indian Ocean sector to Indian summer monsoon rainfall. Clim Dyn 2022;1-21. Doi: 10.1007/s00382-022-06466-z
45. Balbus JM, McCannon CJ, Mataka A, Levine RL. After COP26-putting health and equity at the center of the climate movement. N Engl J Med 2022;386:1295-7.

How to cite this article: Mishra PK, Kumari R, Shandilya R, Ratre P, Bhargava A, Pathak N, *et al*. Reproductomics: An impending driver for exposome research. J Reprod Healthc Med 2022;3:10.