Editorial

Decoding the Environmental Etiology of Non-communicable Diseases

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The global burden of chronic non-communicable diseases (NCDs), such as cardiovascular diseases, diabetes, chronic respiratory diseases, and cancers, constitutes a paramount public health challenge of our time. While genetic predisposition and lifestyle factors are established contributors, a substantial portion of chronic disease etiology remains unexplained[1]. Increasingly, scientific evidence points to the pervasive role of environmental factors—the air we breathe, the water we drink, and the chemicals we encounter—as critical, yet often modifiable, determinants. These environmental exposures can act as initiators, promoters, or aggravators of pathological processes over the life course. Understanding the specific components, timing, mechanisms, and magnitudes of these environmental risks is no longer a niche scientific pursuit but a fundamental prerequisite for moving from disease treatment to true prevention. This necessitates a shift in research focus towards meticulously decoding the complex causal pathways linking environmental insults to chronic health outcomes, thereby informing targeted interventions and policies aimed at reducing the attributable burden.

A key conceptual advancement on the environmental etiology of chronic diseases is the "exposome," which encompasses the totality of environmental exposures from conception onward[2]. This framework drives investigations into the effects of complex real-world mixtures, as highlighted by studies on the varying toxicity of $PM_{2.5}$ constituents like black carbon. Methodologically, there is a strong emphasis on elucidating biological mechanisms. Research now routinely integrates external exposure assessment with internal biomarker measurement (e.g., urinary metabolites of pollutants) and intermediate phenotypic responses (e.g., oxidative stress, inflammation) to construct plausible causal pathways. Furthermore, the integration of novel tools is transformative. Geographic Information Systems (GIS) and satellite-based modelling allow for refined exposure assessment at the population level, while advances in toxicogenomics and epigenetics are uncovering how environmental factors interact with biological systems at the molecular level to influence disease susceptibility.

In China, large-scale epidemiological studies that leverage unique populations and exposure scenarios[3]. Longitudinal cohorts in areas with high air pollution have provided robust evidence on the long-term cardiopulmonary effects of $PM_{2.5}$. Studies also focus on region-specific environmental stressors, such as the health impacts of sandstorm-derived particulates in arid regions and the challenges of indoor air pollution in certain rural areas. China National Human Biomonitoring launched in 2017, to generate authoritative national data on the internal exposure levels to environmental chemicals, and to provides the scientific foundation for assessing environmental etiology and health risks, informing environmental policy[4]. There is a growing effort to bridge evidence with national health initiatives like “Healthy China 2030,” pushing research towards generating actionable knowledge for precision prevention.

Despite considerable progress in the field, substantial scientific challenges continue to hinder a definitive understanding of the environmental origins of chronic diseases. The evidence base is often constrained by a reliance on observational data from cross-sectional studies, which are limited in establishing causality, coupled with a scarcity of long-term longitudinal cohorts needed to identify critical exposure windows across the lifespan. Accurately assessing the full spectrum of lifelong exposures—the exposome—including complex mixtures of chemicals and their potential interactions, remains a significant technical hurdle. Methodologically, persistent issues of confounding, where environmental risks are intertwined with

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socioeconomic and behavioral factors, complicate the isolation of true effects and can lead to biased risk attribution. Furthermore, a translational gap exists; insights from mechanistic toxicology are often not validated with specific biomarkers in human populations, and research findings are frequently not synthesized into actionable evidence for setting protective exposure standards or designing targeted interventions[5]. These interconnected limitations delay the shift from identifying associations to implementing effective, precision prevention strategies in public health.

Future research must build on these foundations to fully decode the environmental etiology of chronic diseases. Several key directions are paramount:

Future research must embrace the complexity of mixed exposures within an exposome framework. Research must systematically assess the combined effects of chemical and non-chemical stressors (e.g., air pollutants, noise, greenspace, socioeconomic factors) within an exposome framework. Advanced statistical methods for mixture analysis and machine learning are needed to identify critical exposure combinations and their interactions.

Strengthening causal inference requires advanced methodologies to move beyond association. Moving from association to causation requires wider adoption of study designs and analytical techniques that minimize confounding and bias. This includes the use of quasi-experimental designs, mendelian randomization, and the development of more specific and validated biomarkers of exposure, effect, and susceptibility[6].

Adopting a lifecourse perspective is essential to map critical windows of susceptibility. Critical or sensitive periods of exposure (e.g., in utero, early childhood) may have durable effects on disease risk later in life. Longitudinal studies starting from pre-conception or early childhood are essential to map these windows of susceptibility.

Linking mechanisms to populations through a "meet-in-the-middle" approach can validate pathways and identify vulnerability. A tighter integration of toxicological mechanism research (using *in vitro* and *in vivo* models) with human epidemiological studies is needed. This "meet-in-the-middle" approach can validate mechanistic pathways in humans and identify population subgroups most vulnerable due to specific biological pathway[7].

Translating science into action is the ultimate goal for precision environmental public health. Findings should inform the development of evidence-based exposure standards, the identification of actionable environmental interventions, and the creation of targeted health guidance for vulnerable communities, ultimately fulfilling the promise of precision environmental public health.

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