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Unravelling the complexity of environmental exposures and health: A novel exposome-centered framework for occupational and environmental epidemiology

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Abstract

The exposome-centered approach marks a significant shift in occupational and environmental epidemiology, prioritizing a holistic evaluation of environmental exposures throughout an individual's life to elucidate their effects on health. Unlike traditional methods that single out environmental factors for their direct health impacts, this approach seeks an integrated analysis of all non-genetic influences, encompassing specific and general external environments and internal responses. While acknowledging environmental factors' pivotal role in chronic diseases and global mortality, existing methods struggle with precisely measuring and analyzing the broad spectrum of exposures and their combined effects. The exposome framework addresses these gaps through advanced omics technologies, refined exposure assessment models, and comprehensive data analytics. Yet, its application faces hurdles like the requirement for substantial infrastructure, cross-disciplinary training, and new statistical techniques for high-dimensional data analysis. Recent endeavors in applying the exposome concept show its promise in improving our understanding of environmental and occupational health, underlining its importance in advancing epidemiological research and public health. This abstract condenses the rationale, challenges, and ongoing efforts to incorporate the exposome into epidemiol-ogical studies, emphasizing its potential in enhancing the field.

Keywords: Exposome; Environmental Exposures; Epidemiology; Multi-omics Approach

1. Introduction

Environmental factors, including air pollution, smoking, and diet, are linked to nearly half of global deaths, yet the interplay of multiple exposures complicates chronic disease understanding (Vrijheid et al., 2020a; Dhimal et al., 2021; Waubant et al., 2019). Traditional epidemiology often misses the complex effects of combined exposures, such as the nuanced impact of ambient particulate matter on cardiovascular disease (Kalia et al., 2022). The challenge is exacerbated by the lack of precise biomarkers for many exposures, hindering effective public health assessments (Proki et al., 2019; Silva et al., 2020).

The EPA emphasizes the importance of environmental factors in major health issues like asthma and cancer, advocating for thorough monitoring and intervention (Jiang et al., 2018). The exposome concept, introduced by Wild in 2005, advocates for a lifespan-wide environmental exposure assessment to enhance epidemiological studies and address the limitations of focusing solely on genetic factors (Wild, 2005; Walker et al., 2019). This approach has received broad

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support for its potential to more accurately account for the cumulative effects of environmental factors (Keil et al., 2020).

Adopting the exposome framework, with its comprehensive strategy for cataloging environmental exposures, is advancing occupational and environmental epidemiology. It encourages the development of novel research methodologies and the integration of diverse environmental health perspectives, from addressing health disparities to linking metabolic profiles with exposures (Daiber et al., 2019; Rager et al., 2020). This shift promises a more integrated understanding of the impact of environmental factors on health.

2. Literature review

2.1. The Exposome-Centered Framework

The concept of the 'exposome,' introduced by (Wild C.P., 2005) captures all environmental exposures, including non-genetic factors from conception, to complement genetic research (Catalán et al., 2022). Aimed at addressing the need for comprehensive environmental exposure data, the exposome concept balances the focus on genetics with environmental factors (Guloksuz et al., 2018). It encompasses three overlapping domains: (1) the general external environment, covering urban settings, climate, social factors, and stress (Tamiz et al., 2022); (2) the specific external environment, detailing pollutants, diet, physical activity, tobacco use, and infections (Daiber et al., 2019); and (3) the internal environment, including metabolic processes, gut microbiota, inflammation, and oxidative stress (Finch & Kulminski, 2019). Mapping every exposure over a lifetime presents challenges, requiring continuous integration of various internal and external exposures across an individual's life course (Gao, 2021).

2.2. The External Exposome

The exposome concept highlights the difficulty in measuring varied environmental exposures affecting health, such as those related to asthma, including both indoor and outdoor pollutants, and lifestyle factors (Hu et al., 2021; Santos et al., 2020). It distinguishes between specific exposures like tobacco smoke, assessed through questionnaires, and general exposures like air pollution, evaluated via geographical methods (Shiels et al., 2021; Martin & Fry, 2018). Integrating predictive models, biomarkers, and monitoring enhances exposure assessment, validating self-reported data and improving the understanding of how exposures impact health, particularly in asthma studies (Waubant et al., 2019; Robinson et al., 2018).

Technological advancements, such as smartphone-connected diaries and air pollution measurements, facilitate detailed exposure tracking, combining data on diet, product use, and physical activity. These tools enable better community-level exposure assessment by capturing precise location, movement, and inhalation rates, key to accurately estimating inhalation doses and characterizing the external exposome (Barupal & Fiehn, 2019; Nieuwenhuijsen et al., 2019).

2.3. The Internal Exposome

Recent advances in omics technologies have significantly enhanced the study of biological molecules, enabling comprehensive analysis of metabolites, proteins, gene expression, and epigenetic modifications induced by environmental exposures (Fang et al., 2021; Jiang et al., 2018). These advancements have highlighted the role of epigenetic changes, such as methylation and miRNA modifications, in response to toxicants (Barouki et al., 2022). Although omics applications in human studies are still emerging, they show promise in predicting health risks related to environmental exposures and individual vulnerabilities (Niedzwiecki et al., 2019).

Examples include methylation profiles linked to air pollution and smoking, metabolomic impacts of diet, and protein effects from benzene, arsenic, and lead exposure (Walker et al., 2019). Omics techniques aim to identify biological response signatures to complex or cumulative exposures, potentially offering a holistic approach to characterize the exposome akin to DNA sequencing in genetic studies (Vermeulen et al., 2020; Zhang et al., 2021). Traditional biomarkers, limited by cost and sample size, are being surpassed by the broad scope of omics data, which can uncover new risk factors and elucidate molecular mechanisms of exposure-related health outcomes (Vrijheid et al., 2020). However, implementing omics in environmental and occupational health research faces challenges in study design, validation, and analysis (Tang et al., 2021).

2.4. The Dynamic Exposome

The exposome encompasses all environmental exposures throughout an individual's life, differing from the stable genome by being highly dynamic, with exposures changing from momentary to lifelong scales (Gracia-Cazaña et al., 2020; Nwanaji-Enwerem et al., 2021). A single measurement falls short of capturing the full scope of these influences on health, highlighting the need for innovative study approaches (Liu et al., 2023).

Focusing on critical life stages, such as prenatal and early childhood, which are particularly sensitive to environmental factors, is one strategy for studying the exposome. These periods are pivotal for the onset of diseases like allergies and respiratory conditions, guiding efforts toward prospective birth cohort studies to analyze the exposome during early development (Daiber et al., 2019; Maitre et al., 2022).

Another method involves applying the exposome concept across multiple cohorts covering different life stages, offering a broader perspective on the accumulative and long-term health impacts of environmental exposures. This approach seeks to provide a more complete understanding of the exposome's role in influencing health across the lifespan (Haddad et al., 2019).

3. The exposome-centered framework for health

The exposome-centered framework, focusing on a wide array of chemical, physical, and molecular data, necessitates robust data management and analytical strategies to decipher complex environmental impacts on health (Barouki et al., 2018). Traditional single-exposure regression models are being complemented by innovative approaches to handle the multiplicity and interaction of exposures. One such approach is the "environment-wide association study" method, which agnostically identifies key risk factors for diseases like type 2 diabetes and mortality, generating hypotheses for further investigation (Sillé, 2020). Data-driven dimension reduction techniques offer another method by condensing data to retain essential information, facilitating the analysis of combined exposure effects on health (González-Domnguez et al., 2020). Bayesian profile regression, analyzing risk estimates for groups with similar exposomes, allows for the assessment of cumulative exposures and their interactions within a population (Panagopoulos-Abrahamsson et al., 2021). For policymaking, systematic health impact assessments are crucial, moving beyond one-dimensional models to incorporate a comprehensive view of multiple exposures and outcomes. This shift aims to equip decision-makers with a nuanced understanding of policy impacts on health, integrating risks and benefits within a holistic framework and acknowledging the complexity of exposome-health relationships (David et al., 2021; Zhang et al., 2021; Vineis et al., 2020).

4. Rationale for the exposome research within occupational and environmental epidemiology

The exposome framework broadens the scope of environmental and occupational health research, moving beyond traditional single-exposure studies to consider the full spectrum of environmental interactions over an individual's lifetime. It addresses the inadequacy of analyzing health effects through a one-chemical-at-a-time lens, advocating for a comprehensive evaluation of multiple exposures (Sun et al., 2022; Vineis et al., 2020; Safarlou et al., 2023).

This approach necessitates a variety of assessment methods to accurately capture the dynamic and complex nature of exposures, from biosampling to environmental monitoring (Patel, 2019; Haddad et al., 2019). By examining exposures across different life stages and contexts, the exposome framework identifies sensitive periods and the cumulative impact of environmental factors on health, employing hierarchical data analysis to explore exposures at multiple levels (Gao & Snyder, 2021; Catalán et al., 2022).

The inclusivity of the exposome model presents challenges in managing confounders due to the broad range of considered factors, necessitating refined data collection methods to differentiate between environmental influences and non-environmental confounders (Santos et al., 2020; Shiels et al., 2021). The framework enhances epidemiological rigor by ensuring comprehensive exposure assessment, minimizing bias and measurement error, and facilitating the exploration of novel associations between the environment and health outcomes (Niedzwiecki et al., 2019; Fang et al., 2021).

Exposome research underscores the importance of adhering to epidemiologic principles and requires bioinformatic analysis and validation of findings in subsequent studies, positioning the exposome as a complementary approach to hypothesis-driven research in environmental health (Gao, 2021; Barouki et al., 2022; Sillé, 2020).

5. Implementation of epidemiological methods relative to the exposome

Implementing epidemiological methods within the exposome framework involves characterizing the exposome and linking it to health outcomes. Research often focuses on sensitive periods like fetal and early childhood development, where exposure impacts are profound. Various studies illustrate this approach:

Maternal Exposome and Birth Outcomes: Examines the effects of maternal exposome during pregnancy on outcomes like preterm birth and low birth weight, aiming to identify harmful exposures and mechanisms (Haddad et al., 2019).

Developmental Exposome and Neurodevelopment: Investigates how prenatal and early childhood environmental factors influence neurodevelopmental disorders, including Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactive Disorder (ADHD) (Vrijheid et al., 2020b; Gracia-Cazaña et al., 2020).

Early Life Exposome and Respiratory Health: Studies the relationship between early life environmental exposures and respiratory conditions such as asthma, focusing on allergens, pollutants, and microbial agents (de Prado-Bert et al., 2021).

Exposome and Chronic Disease Risk: Looks at how lifelong exposure to environmental factors affects the risk of chronic diseases like cardiovascular disease and diabetes (Gao & Snyder, 2021; Patel, 2019).

Exposome and Epigenetic Modifications: Explores how environmental exposures induce epigenetic changes that influence disease susceptibility across the lifespan (Safarlou et al., 2023; Sun et al., 2022).

These studies, along with funding for projects like the European Union's Framework Program and efforts like the Japan Environment and Children's Study (JECS) and the US NICHD's LIFE project, highlight the evolving integration of exposome measures into epidemiologic research. The LIFE project, for instance, has begun to uncover associations between environmental exposures and fertility outcomes, employing a broad data collection strategy to facilitate a comprehensive exposome analysis (González-Domnguez et al., 2020; Nieuwenhuijsen et al., 2019).

Environment-wide association studies (EWAS) represent another innovative approach, analyzing a wide range of environmental exposures at specific time points to identify non-genetic factors contributing to diseases like type 2 diabetes. These studies provide a foundation for future research by employing agnostic techniques to detect environmental influences on health (Walker et al., 2019; Vrijheid et al., 2020b; Krenz et al., 2023).

By incorporating these methodologies, researchers aim to deepen our understanding of the exposome's role in health and disease, guiding public health interventions and strategies for a healthier future.

6. Challenges to incorporating the exposome into epidemiologic research

Incorporating the exposome into epidemiologic research faces several challenges, including infrastructure gaps for comprehensive exposure assessments, difficulty distinguishing between normal physiological variations and environmentally induced changes, and a lack of advanced analytical tools for high-dimensional data (Santos et al., 2020; Fang et al., 2021). Additionally, there is a need for interdisciplinary expertise to navigate these complexities (Sillé, 2020).

The exposome's broad scope, encompassing a lifetime of environmental exposures such as air pollution and noise, complicates measurement and quantification. This complexity makes it challenging to pinpoint specific exposures linked to health outcomes and to control for confounders in studies (Daiber et al., 2019; David et al., 2021).

Centralized support and coordination, as demonstrated by the European Initiative and the NIEHS CHEAR centres, have shown promise in advancing exposome research, emphasizing the need for similar investments across various life stages (Robinson et al., 2018; Nieuwenhuijsen et al., 2019). Linking early-life exposome data to adult disease outcomes could provide critical insights into disease mechanisms (Hu et al., 2021).

Effective exposome research requires distinguishing between random variation and significant biological responses, with attention to developmental stages like puberty and pregnancy, which are susceptible to environmental disruptions (Guillien et al., 2021; Nieuwenhuijsen et al., 2019). Despite the impossibility of creating a static reference exposome due to its dynamic nature, efforts to characterize temporal variations in exposures and responses are crucial (Maitre, Bustamante, et al., 2022).

The exposome approach demands significant data storage and sophisticated computational models to handle the variability and interconnectivity of exposures and outcomes across populations and time. This complexity exceeds that of genomic research due to the longitudinal aspect of environmental exposures, highlighting the need for expertise in computer science, bioinformatics, and biostatistics (Kalia et al., 2022; Gudi-Mindermann et al., 2023).

Despite these challenges, the exposome-centered approach offers a promising pathway to deepen our understanding of how long-term environmental exposures influence health, underscoring the potential for significant advancements in public health research and policy.

7. Conclusion

Integrating the exposome-centered approach into epidemiologic research offers insights into the environmental and occupational determinants of health, despite facing challenges like infrastructure deficits and difficulties in analyzing complex data. Progress, exemplified by the Hypothermia for encephalopathy in low and middle-income countries (HELIX) and the Japan Environmental and Children's Study(JECS) studies, demonstrates the feasibility of tracking environmental influences on health. Advancements in supporting infrastructure have facilitated these explorations, particularly regarding early-life exposures.

To further exposome research, it's crucial to refine methodologies for handling the unique challenges of exposome data, including its high dimensionality and the variability of exposures over time. Emphasizing transdisciplinary collaboration and broadening data sharing are key strategies to address the intricate relationships between environmental factors and health outcomes. These efforts aim to propel forward environmental health research, with the goal of improving public health.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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