An exposomic framework to uncover environmental drivers of aging

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Abstract

The exposome, the environmental complement of the genome, is an omics level characterization of an individual's exposures. There is growing interest in uncovering the role of the environment in human health using an exposomic framework that provides a systematic and unbiased analysis of the non-genetic drivers of health and disease. Many environmental toxicants are associated with molecular hallmarks of aging. An exposomic framework has potential to advance understanding of these associations and how modifications to the environment can promote healthy aging in the population. However, few studies have used this framework to study biological aging. We provide an overview of approaches and challenges in using an exposomic framework to investigate environmental drivers of aging. While capturing exposures over a life course is a daunting and expensive task, the use of historical data can be a practical way to approach this research.

Keywords: exposome; aging; hallmarks of aging; population-based studies of aging; measuring the exposome

Introduction

The human body reacts constantly to changes in its environment. Microbial invasions induce immunological responses [1]; social threats trigger the neuroendocrine cascade of the stress response [2] and can alter immune stance [3]; toxin, toxicant, and pollutant exposures elicit protective responses across multiple systems [4] and can induce adverse effects [5]; and change in ambient temperature can disrupt homeostasis [6]. On a cellular level, actions are taken every second based on signals received from the environment. Several factors can influence the effect of these exposures and the body's response, importantly, the levels of certain nutrients, and the overall nutritional status [7]. Environmental signals driving changes in our biology are constant while being variable in space and time [8]. Traditionally, scientists have studied the influence of the environment on human health using a reductionist approach, exploring the effect of a single environmental exposure on a health outcome. However, the recent emergence of the exposome concept provides an alternative framework to holistically study the environment. The exposome encompasses all exposures, throughout the life course [9], and includes internal processes, like endogenous metabolism and microbial-derived metabolites, specific external exposure, like exposure to toxic environmental chemicals and dietary nutrients, and wider social factors that can influence an individual, like financial status and education [10]. It represents the environmental complement to the genome, that is, a comprehensive characterization of the molecular exposures to which an organism is subject [11-13]. For the purpose of this review, we define the exposome as all exposures, including lived experiences, that can be assessed throughout the life course, but recognize the need to focus on those exposures that can be measured with current technologies. We focus primarily on toxic exposures but we acknowledge other important factors that can influence the exposome or the body's response to exposure, such as: (i) nutritional status [7] and the microbiome [14] and (ii) other factors of the external exposome such as education [15] and family environment [16]. While there have been some attempts at characterizing the biological footprint of these factors [17], they remain difficult to measure. Newer studies provide hope and directions on how these factors may be tested in the future [18].

The many chronic diseases of aging are thought to derive from common underlying processes that precipitate molecular changes over time [19]. These common mechanisms have been classified into nine hallmarks of aging: genomic instability, epigenetic alterations, telomere attrition, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication [20]. Aging is influenced by genetic factors [21]; however, current estimates are that <10% of differences in longevity between individuals can be attributed to inherited genes [22]. Environmental factors are therefore critical determinants of aging processes [23].

The exposome and aging

The human body can activate compensatory pathways that provide a form of resilience against damaging factors that accumulate with age. It is proposed that individual differences in this process of resilience determine whether a life course would end relatively healthy, frail, or in early mortality [24, 25]. Adverse

environmental exposures can induce damage and impose additional stress on resilience processes, reducing the reserve needed to counter the effect of biological aging, thus, increasing the risk of poor or accelerated aging.

Time is an important variable that can influence the effect of environmental exposures. Both the timing of exposure during a life course as well as the duration of an exposure can determine the physiological response. It is important to identify critical time windows of exposure across the life course that might influence an outcome of interest since the scale of the response to an exposure would depend on whether the exposure occurred in utero, during development, in mid-life, or later in life [26, 27]. Damaging environmental exposures may be for a short period of time (an acute exposure) or over a prolonged period (a chronic exposure). The response to an acute or transient exposure may subside once the exposure has been removed from the system through metabolism and excretion but may leave signs of lasting damage that can be detected through molecular probes, like epigenetic marks of exposure to cigarette smoke in former smokers [28] or epigenetic changes in immune cells in response to pathogenic exposure [29] whereas response to a chronic exposure is usually maintained to counter the effects of long-term exposure. Thus, exposures may induce temporary or permanent changes in molecular pathways. Both aspects of time can influence whether damage is caused and the organism's response to the exposure.

Several studies have reported associations between environmental exposures and different hallmarks of aging. For example, exposure to air pollution [30], pesticides [31], heavy metals [32], industrial solvents [33], and viruses and bacteria [34] has been associated with mitochondrial dysfunction but no study has investigated the effect of their concomitant exposure on mitochondrial function. Different environmental exposures are correlated, for example, people who live in polluted places tend to lead stressful lives and have reduced access to healthy nutrition, exercise, and leisure. For this reason, studying any one exposure may (a) confuse the apparent effects of the specific exposure with some other, correlated exposures and (b) fail to capture the myriad of exposures that represent the actual environmental burden. In order to illustrate the contributions of various exposures to hallmarks of aging, we have organized observed associations between exposures and the hallmarks of aging (Figure 1). This was created by first categorizing exposures into nine classes: air pollution, pesticides, metals/metalloids, mutagens, industrial solvents, plasticizers and related compounds, ambient temperature, microbes, and cigarette smoke. Each of these categories can comprise of multiple exposures and are grouped due to similarity in source, or chemical structure or properties. In order to confirm an association between the exposure class and a hallmark of aging, we ran multiple searches in PubMed using a combination of the name of each chemical category and, "aging," "hallmarks of aging," or "toxicity." The figure illustrates that different environmental exposures affect many different hallmarks of aging; therefore, an exposomic framework is needed to study environmental drivers of aging. Additionally, the influence of the exposome on the aging process would be modified by the underlying nutritional status and needs to be studied under these contexts [7, 35]. To the best of our knowledge, studies of aging have rarely adopted an exposomic framework.

Measuring the exposome

Compiling exposomic data requires integrating information from multiple sources. Broadly, the sources of data can be geospatial in origin or from personal monitoring [11, 36, 37].

"Geospatial data" can be used to infer individual-level exposure from ecological data. Using data describing the spatial distribution of a toxicant, an estimate of an individual's exposure to that toxicant can be made using their residential address. These data have been used to estimate exposure to air pollution, pesticides [38], access to green space, proximity to pollution sources, proximity to a contaminated water source, and proximity to landfills [39–41]. Data needed to measure the spatial distribution of a toxicant come from:

a) *Satellites* in Earth's orbit which provide valuable information about the Earth's land surface, oceans, and atmosphere. Using optical density, radiation, and imagery data generated through satellite technology, researchers have been able to provide estimates of exposure to pollutants in the atmosphere, humidity, temperature, light exposure at night, even exposure to wildfires [42, 43]. Significant advances in the use of satellite data continue to be made, providing a means to get highly granular historical exposure data [44].

b) *Ground-based monitors and sensors* distributed through national and regional networks have traditionally been used to monitor levels of various air pollutants and provide valuable data that can be used to attribute exposure to study participants using kriging methods [18, 19, 45]. The introduction of low-cost and mobile sensors has made it possible to add more nodes to the network of monitors and provide more granular estimates of air quality [46, 47].

"Personal monitoring data" provide individual-level exposure assessment that can be made through several methods:

a) *Records and surveys* like the national health and nutrition examination survey, census surveys, records maintained by social services and criminal justice administrations, or personal records made through population studies can provide valuable information related to diet, lived experiences, adverse childhood experiences, and psychosocial stress. Census data and other administrative survey data can also be used to determine neighborhood level characteristics, like the racial/ethnic composition of a neighborhood [48, 49]. Personal health records, like electronic health records (EHRs), also provide a means to estimate exposures on a personal level, such as exposure to pharmaceutical drugs, recreational drugs, alcohol, or cigarette smoke. EHR also provide the aging relevant outcome data [50].

b) *Wearable devices and smartphones* have made it possible to make personalized estimates of exposure. Data collected through accelerometers, GPS devices, and wearable sensors provide better estimates of individual level exposure [8, 51, 52]. This data can overcome issues related to geo-spatial data that do not account for movement and activity outside of the residence; however, most methods still need rigorous validation [53].

c) *Biological samples* like blood, urine, sweat, saliva, feces, hair samples, or toenails provide a means to measure the burden of chemical exposures in an individual as well as the biological response as the result of an exposure. Improvements in high-resolution mass spectrometry instruments have made it possible to capture a large proportion of persistent pollutants in a tissue sample using appropriate chromatography [54]. Rapid progress in chemoinformatic software is improving confidence in annotations and expanding the known chemical space [55–57]. The relative levels of different chemicals in a biological matrix are a function of the time since
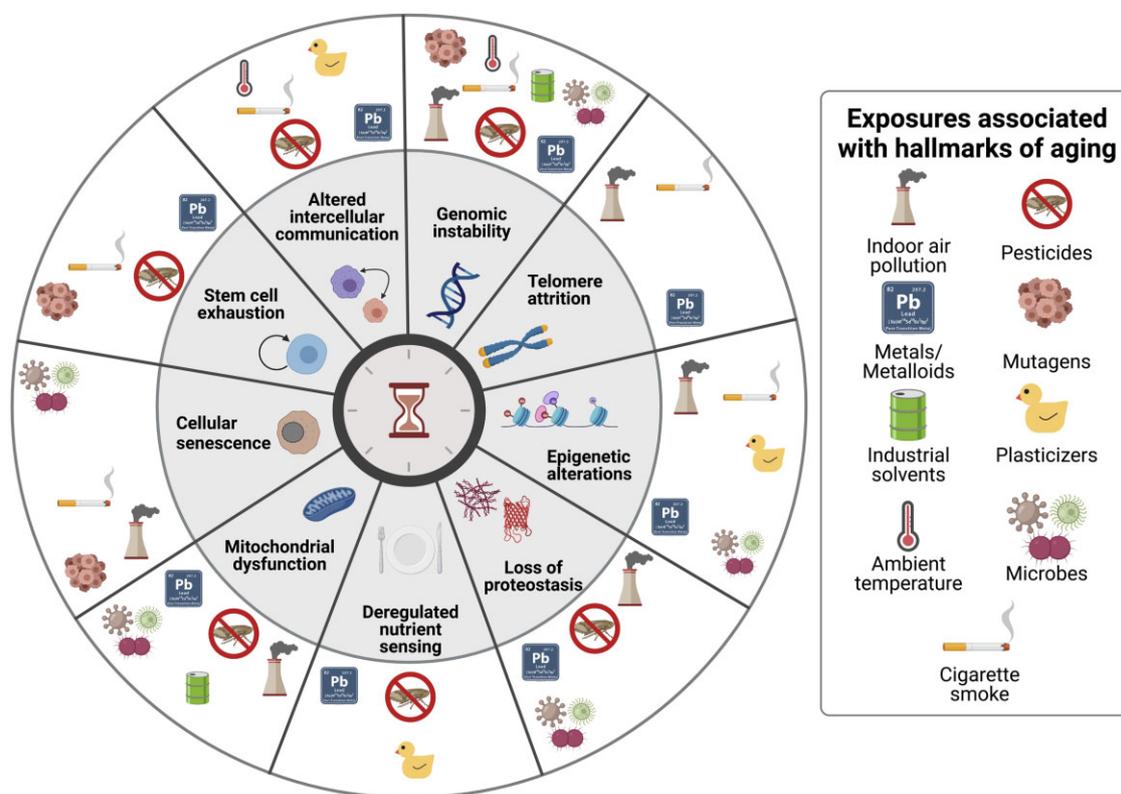
Figure 1. A selection of environmental exposures and hallmarks of aging. The nine hallmarks of aging represent common mechanisms of biological aging in the mammalian context. The inner most gray circle illustrates these hallmarks of aging. In the outer circle, icons represent environmental exposures that have been associated with each corresponding hallmark of aging. Each category can comprise of multiple exposures and are grouped due to similarity in: source, use, chemical structure or properties, or associated health effects. Created with BioRender.com

exposure, the half-life of the chemical in various biological compartments, and the method used to detect and measure the chemicals [58].

These data sources enable measuring exposures on a national, regional, or individual level, and at specific time points in a life course. In this paper, we provide an overview of how an exposomic framework could be applied to studies of environmental drivers of aging. We also illustrate the utility of model organisms to follow up observations made in epidemiological settings.

An ideal scenario

While a randomized clinical trial (RCT) is the gold standard design to uncover causal associations, it is unethical to conduct RCTs of exposure to many environmental toxicants. Instead, the scientific community relies on quasi-experimental observational studies. In order to apply an exposomic framework, study designs that are disease-agnostic and focused on generating a representative sample of the population of interest to enable hypothesis-free analysis of a broad range of exposure will be critical. There are several ways this could be achieved. One possibility is to create birth cohorts that are prospectively observed through their life course [59] with the following considerations:

i) The cohorts should be representative of the target population of interest with representation of marginalized communities within the target population.
ii) Tissue samples should be collected at birth, including the meconium, placental tissue, dried blood spots, maternal blood, and cord blood, in order to assess developmental

origins of health and disease [60]. Biological samples should be collected over the course of development and adulthood. These matrices should be analyzed for: levels of environmental chemicals using high-resolution mass spectrometric techniques and characterization of genomic, epigenomic, extracellular vesicular properties, proteomic, and metabolomic status. An important variable to consider when collecting these matrices would be the unit of time at which this data should be collected [8].

iii) Exposure data associated with each individual in the cohort could be collected using multiple methods described earlier (Figure 2), ideally at fine-grained spatial and temporal resolution. This requires continuous updating of residence information and may also involve harmonization of exposure data across different types of monitors. Attention should also be paid to adverse childhood experiences and lived experiences, which can be collected through questionnaires [61].

iv) Wearable devices and sensors in the homes of participants should also be deployed to provide real-time exposure data to supplement the ecological level exposure data derived from geospatial linkages [8].

A realistic scenario

Birth cohorts are expensive, resource intensive, and prone to attrition. A complementary approach to investigate the exposome in an aging context can leverage existing infrastructure and data. Indeed, population-based cohorts with representation of different age windows are critical for an unbiased exploration of the

Figure 2. Data sources for exposure assessment. For each exposure that has been associated with hallmarks of aging listed in the first column, the corresponding source of exposure data is represented by icons along the row. Created with BioRender.com

exposome. Over decades, several cohort studies have been established that can provide the necessary data for this (Table 1). By creatively using existing data, for example, leveraging natural experiments created through changes in policies [62, 63], we can allocate resources toward the infrastructure needed to characterize the exposome, such as creating exposomic profiles of biological samples available in existing cohorts [64, 65]. Apart from integrating exposure estimates to cohort studies, it will be also be beneficial to consider ways to integrate data across cohorts representing different time points in the life course. This could be achieved by conducting parallel analyses that draw samples from cohorts at the different life course stages, like those conducted under the HELIX project in Europe [66] and in a study that leveraged data from people exposed to Arsenic in Chile and Bangladesh [67].

When using existing resources, some considerations include:

i) Sample storage: When using banked samples, the stability of toxicants and their metabolites should be considered. Even when samples are stored in −80°C freezers, plasma-metabolite levels show storage-time-dependent changes [95].

ii) Half-life of toxicant: Persistent environmental chemicals have long half-lives in the body whereas non-persistent chemicals are metabolized and excreted more quickly [58]. This may limit the type of chemical exposures that can be probed using banked samples that are not collected to specifically capture non-persistent exposure. By leveraging multiple biological matrices representing different biological compartments (urine, blood, saliva, and feces), we can theoretically improve coverage of the chemical exposome.

iii) Data harmonization: Using administrative data, residential address and history information, personal GPS data from mobile applications, and historical geospatial and satellite data, we can estimate historical and present-day exposures to several environmental factors. This data integration is no easy task. We face challenges in harmonization across different exposure estimation methods.

iv) Privacy: It is important to also be aware of privacy concerns that may prevent study participants from sharing personal spatial data [96]. To successfully implement the use of geospatial data, researchers must convey and use methods to protect geoprivacy and disaggregate identifiable information while remaining analytically sound [97]. Further, the methods needed to access and integrate geospatial data with outcomes will differ based on population contexts [98], for example, integrating data in countries with universal health coverage will need methods different from those needed in other contexts. The readers are directed to papers by others in the field to choose an approach that protects geoprivacy [99, 100].

v) Statistical considerations: Studying the relationship between measures that are time varying, like the exposome, and biological changes over time seen in aging poses several analytical challenges. Depending on the nature of the aging outcome, statistical methods that can be applied in these settings include: mixed-effects models [101], cox

Table 1. A selection of population-based studies of aging well-suited to investigate the exposome

Resource	Location/cohort	Tissue type/biomarkers	Environmental data	Sample size/age range	Reference
Gateway to global aging data	US Health and Retirement Study; Mexican Health and Aging Study; English Longitudinal Study of Ageing; Study of Health, Ageing and Retirement in Europe; Costa Rican Longevity and Healthy Aging Study; Korea Employment Information Service; Japanese Study of Aging and Retirement; The Irish Longitudinal study of Ageing; The China Health and Retirement Longitudinal Study; The Longitudinal Study in India; Malaysia Ageing and Retirement Survey; Health, Aging, and Retirement in Thailand; The Brazilian Longitudinal Study of Aging; Northern Ireland Cohort for the Longitudinal study of Ageing; Healthy Ageing in Scotland; The Health and Aging Study in Africa; Study on Global Ageing and Adult Health; Indonesia Family Life Survey	Varies by cohort. The reader is encouraged to visit this resource for information: https://gero.usc.edu/cbph/network/studies-with-bio markers/	Residential address, questionnaires	The sample size varies by cohort and ranges from ~3000 to ~70 000 at baseline. The age eligibility varies by cohort and ranges from 40 to 60 years.	https://g2aging.org/
Centre for Longitudinal Studies	1958 National Child Development Study, 1970 British Cohort Study, Next Steps, Millennium Cohort Study	Blood	Questionnaires	The sample size varies by cohort but ranges from 16 000 to 19 000. The age varies by cohort.	https://cls.ucl.ac.uk/
The UK Household Longitudinal Study	United Kingdom	Blood	Questionnaires	In Wave 1, surveyed 40 000 households. Includes people of all ages.	[68]
The Rotterdam Study	Netherlands	Blood	Questionnaires	Sample size of 15 000. Age >45 years.	[69]
The Leiden Longevity Study	Netherlands	Blood	Questionnaires	Surveyed 421 families. Age criteria ≥89 for men and ≥91 for women	[70]
The Lothian Birth Cohorts	United Kingdom	Blood	Questionnaires	The two birth cohorts had an initial (Wave 1) sample size of 550 and 1091. Age >69 years	[71]
Cooperative Health Research in the Augsburg Region (KORA)	Germany	Blood	Geospatial data, questionnaires	Sample size of 18 000. Age range 25–74 years	[72]
The European Prospective Investigation into Cancer and Nutrition	Europe	Blood	Questionnaires	Sample size of 521 000. Age range 35–70 years	[73] https://epic.iarc.fr/ about/studyresour ces.php
Longitudinal Aging Study Amsterdam, GECCO, and MINDMAP study	Netherlands	Blood	Geo-coded data, questionnaires	Initial sample size of 3805. Age range 55–84 years	[74–76]
Jerusalem Longitudinal study	Israel	Blood, serum, urine	Residential address, questionnaires	Initial sample size of 605 Representative of those 70-years old.	[77]
Cambridge city over 75 s cohort	United Kingdom	Blood and saliva	Residential address, questionnaires	Sample size 2600 Age >75 years	[78]

Table 1.. (continued)

Resource	Location/cohort	Tissue type/biomarkers	Environmental data	Sample size/age range	Reference
Cognitive Function and Aging studies	United Kingdom	Blood	Residential address, questionnaires	Sample size >18 000 Age >65 years	[79]
GAZEL cohort	France	–	Occupational exposure, residential address, questionnaires	Sample size >20 000 Age >35 years	[80]
Helsinki Health study	Finland	–	Occupational exposure, residential address, questionnaires	Sample size >9000 Age range 40–60 years	[81]
All of us Research Program	United States	Blood, saliva, urine	Wearable sensors, residential address, questionnaires, EHR	Aim to enroll at least 1 million people Age >18 years	[82]
UK Biobank	United Kingdom	Blood, saliva, urine	Wearable devices, residential address, questionnaires, EHR	Sample size of 500 000 Age >40 years	[83]
Washington Heights and Inwood Community Aging Project	United States	Blood	Residential address, questionnaires	Sample size >4000 Age >65 years	[84]
Multi-Ethnic Study of Atherosclerosis (MESA) and MESA Air	United States	Blood	Residential address, air pollution estimates, questionnaires	Sample size of 6814 Age range 45–84 at enrollment	[85, 86]
Mediators of Atherosclerosis in South Asians Living in America	United States	Blood, urine	Residential address, questionnaires	Sample size of 906 Age range 40–79 at enrollment	[87]
The London Life Sciences Prospective Population Study	United Kingdom	Blood	Residential address, questionnaires	Sample size ~28 000 Age range 35–74 at enrollment	[88]
Normative Aging Study	United States	Blood	Residential address, questionnaires	Initial sample size of 2280 Mean age at enrollment 42 years	[89]
Women's health initiative	United States	Blood	Residential address, questionnaires	Sample size >161 000 Age at enrollment 50–79 years	[90]
Strong Heart Study	United States	Blood, urine	Questionnaires	Sample size >7600 Age at enrollment 35–74 years	[91]
Baltimore Longitudinal Study of Aging	United States	Blood, urine	Residential address, questionnaires	Sample size >3200 Age >20 years at enrollment	[92]
Coronary Artery Risk Development in Young Adults Study	United States	Blood, urine	Residential address, questionnaires	Sample size >5000 Age at enrollment 18–30 years	[93]
Rush Memory and Aging Project	United States	Blood	Residential address, questionnaires	Initial sample size 1556 Mean age ~81 years	[94]

Many population studies of aging exist that can be used to study environmental drivers of aging using an exposomic framework. A selection of them are shown here. GECCO, Geoscience and Health Cohort Consortium and GAZEL, GAZ and ELectricité.

proportional hazards models [102], survival analyses [103], multi-state modeling techniques [104], or age-period-cohort modeling [105]. Besides handling temporal dynamics, the high-dimensionality of exposomic data needs to be treated with appropriate statistical methods [106]. Several papers have been written that describe new methods for analyzing time-varying, high-dimensional data [59].

vi) Survival bias/mortality selection: Observations of older adults include only those individuals who have survived to advanced ages. Exposomic parameters that are more lethal may be under-represented in the oldest members of research cohorts [107]. Thus, studies that are truly representative of the population are crucial to understand real-world exposures.

vii) Misclassification: Researchers must conduct sensitivity analyses to determine the effect of exposure misclassification or error in predictions based on sparse historical data, or other decisions and assumptions made during exposure estimation. Systematic errors that differentially affect exposure measurements in sub-groups of populations may introduce bias in analyses, for example, people with unstable residences may be assigned imprecise measures of exposure.

viii) Study design limitations: When using a design that is a mixture of prospective and retrospective measurement, researchers would need to consider the limitations that are inherent to such a design, such as recall bias and reverse causation [36].

Toxicological follow-up

Many aspects of biological aging were first discovered in model organisms *Caenorhabditis elegans* and *Drosophila melanogaster*. Model organisms remain an important tool in uncovering mechanisms of biological aging and to discover interventions. These models can also play a role in understanding biological plausibility and gradient, which are part of Hill's causal criteria [108], of any significant findings in observational settings.

The long history of *C. elegans* in genetic and neuroscience research provides a rich resource in the pursuit of environmental drivers of aging. The large number of existing mutant libraries provides limitless opportunity and their genetic tractability makes them useful models to find as yet uncharacterized relationships between exposures and genetic susceptibility. *Caenorhabditis elegans* are amenable to high-throughput screens and have been used by the National Toxicology Program for this purpose [109]. Studies have found good correspondence between LD_{50} values of several toxicants in rodents and *C. elegans* [110]. An example of the type of high-throughput approaches is the COPAS biosorter, which is a flow cytometer that can handle particles as large as *C. elegans*. The instrument has been used to screen for reproductive and neurodegenerative toxicants [111–113].

Over decades, researchers have developed several open source methods that favor the use of *C. elegans* in aging research. For example, the lifespan machine developed by Stroustrup et al. [114] makes it possible to measure the lifespan of thousands of worms with significantly reduced human involvement. As another example, several researchers have developed methods to study associative memory in the organism [115]. Additionally, researchers are able to characterize tissue-specific gene expression [116], miRNA expression [117], histone modifications [118], and global

metabolism [111, 119]. They are also excellent models to study reproductive aging and development [113, 120].

Data from whole organisms can be complimented by predictive toxicology, which may provide evidence of exposure, metabolism, absorption, and potential toxic effects of exposure using computational methods. The adverse outcome pathway (AOP) framework has been used to improve mechanistic understanding and to predict adverse effects of exposure using existing toxicological evidence [121]. While the use of AOP framework has generally been limited to individual chemicals, experts have recommended its use in exposome research by moving from linear pathways to networks of pathways, thus considering multiple causes for adverse effects [122]. The use of AOPs in the exposome context can help create *a priori* mechanistic links between exposure to mixtures and adverse outcomes relevant to the aging process [123].

Measures of aging

The molecular hallmarks of aging [20], established from studies of cells and model organisms, are difficult to measure in studies of humans. As a result, there remains no gold standard measure of human aging, although a range of demographic, clinical, and molecular methods have been proposed [24, 124]. In demography, researchers quantify aging at the population level from differences in mortality rates across chronological ages [125]; in clinical gerontology, researchers quantify aging at the patient level from accumulations of chronic diseases and functional deficits [126] and measures of physical frailty [127]; in the emerging field of geroscience, which seeks to translate basic science in the biology of aging to prevent chronic disease [19, 128], researchers quantify aging using algorithms that summarize omics data to estimate the state or pace of decline in system integrity, referred to as biological aging [129–131]. None of these outcomes has yet received substantial research attention in an exposomic framework. However, early studies investigating impacts of environmental pollutants suggest substantial promise [132–135].

Similar to the exposome, these processes change over time, that is, they evolve over decades. This creates the challenge of intersecting dynamic exposures to dynamic biological processes, especially since we are interested in understanding when biological aging deviates from chronological aging.

Conclusion

With a rapidly aging global population, understanding the drivers of aging is more important than ever before. The exposome framework is responsive to the reality of human exposures, they are variable in space and time, and occur concomitantly. In the paper, we have described some ways in which the exposome framework could be applied to aging research; however, challenges remain in capturing profiles of chemicals with: short half-lives, low abundance in the body, and those present in a minor subset of the population. Despite these limitations, using an exposomic framework can provide a realistic assessment of major environmental drivers of aging, providing a means to prioritize policies and interventions that can prevent unhealthy aging. Birth cohorts should be set up in several locations worldwide to ensure representation of low- and middle-income countries. International projects like the 1000 genomes project or the HAPMAP project may provide a valuable template to create exposomics profiles in populations across the globe [136, 137]. The availability of high-quality assessment of molecular hallmarks of aging is critical to studying environmental

drivers of aging and resources must be directed at improving read-outs of hallmarks of aging. Integration of historical environmental exposure data with existing population studies has the potential to accelerate this research agenda.

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Dr. Miller receives royalties from his books The Exposome: A Primer and The Exposome: a New Paradigm for the Environment and Health. He also receives an annual stipend for his service as Editor-in-Chief of Exposome.

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