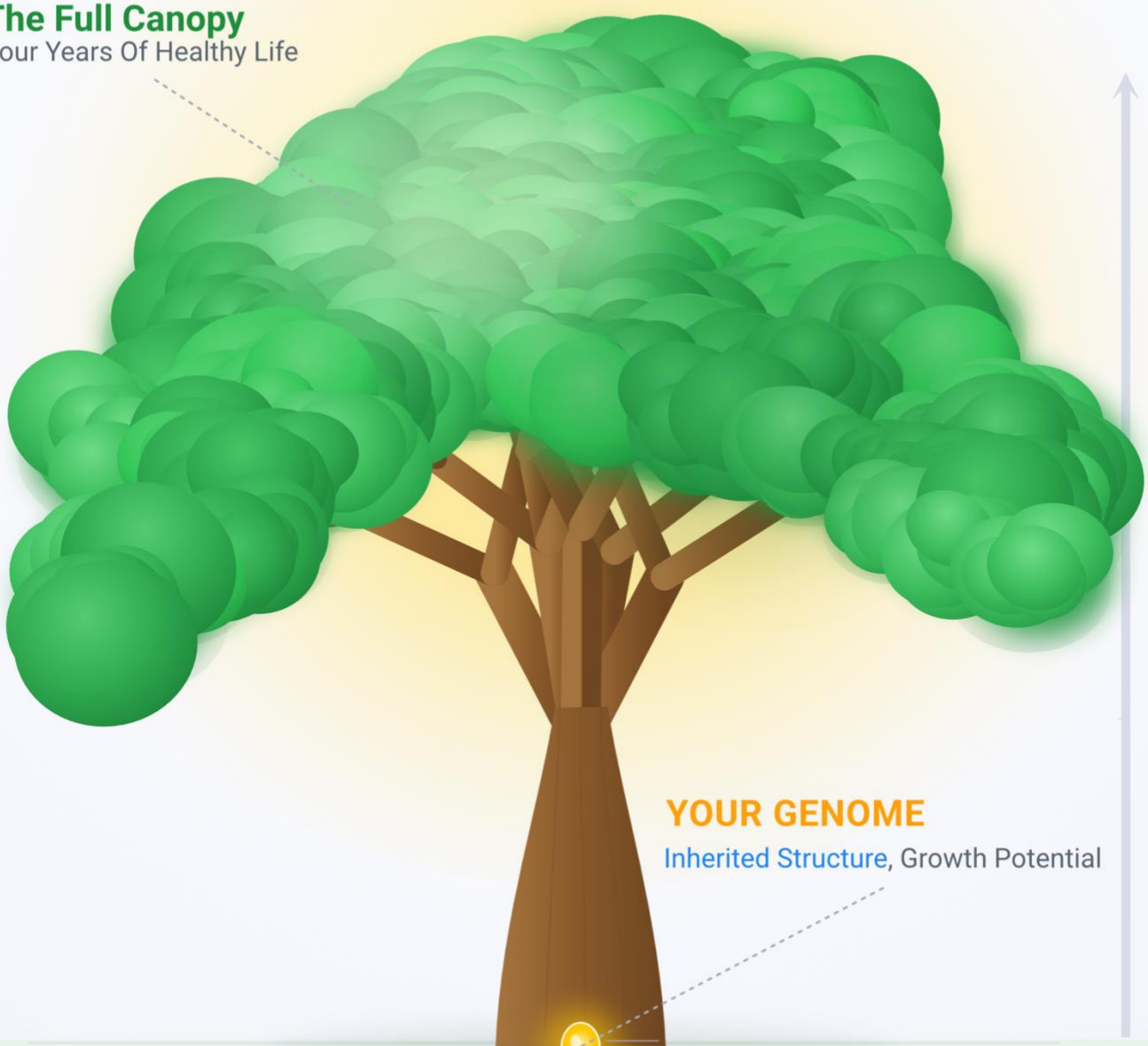
HEALTHSPAN HORIZONS

The Exposome & Healthspan

The Missing Layer of Precision Health

Your Exposome
Soil • Air • Sun • Environment

The Full Canopy
Your Years Of Healthy Life



HEALTHSPAN
Height & Canopy = Years Of Healthy Life

YOUR GENOME
Inherited Structure, Growth Potential

AIR	DIET	MOVEMENT	SLEEP	STRESS	PLACE
What You Breathe	What You Eat	How You Move	How You Rest	What You Feel	Where You Live

YOUR EXPOSOME

A Lifetime Of Environmental & Lifestyle Inputs The Roots Drink

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Buck Institute for Research on Aging

Your genome sets the starting conditions. Your exposome shapes how you grow.
Tend the soil, and the canopy of healthy years grows with it.

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What's inside

SECTION 01 · HEALTHSPAN HORIZONS

We Do Not Age in Isolation

Our aging is strongly dependent on the environments we breathe, drink, eat, and socially inhabit. Every day, the air we breathe, the water in our glass, the chemicals in the products we touch, the heat we experience, and the rhythms of our work and rest are writing themselves into our biology. These exposures — collectively known as the exposome — shape how fast we age, how well we recover, and how long we stay healthy.

Historically, medicine has searched for the causes of health and disease primarily inside the body — in our genes, our cells, and our clinical biomarkers. That search has been extraordinarily productive, but it has also been incomplete. The genome tells us what is possible. It does not, by itself, tell us what is actually happening to our health or the triggers that move us from health to functional decline. Those factors are determined largely by the world around us and how we interact with it.

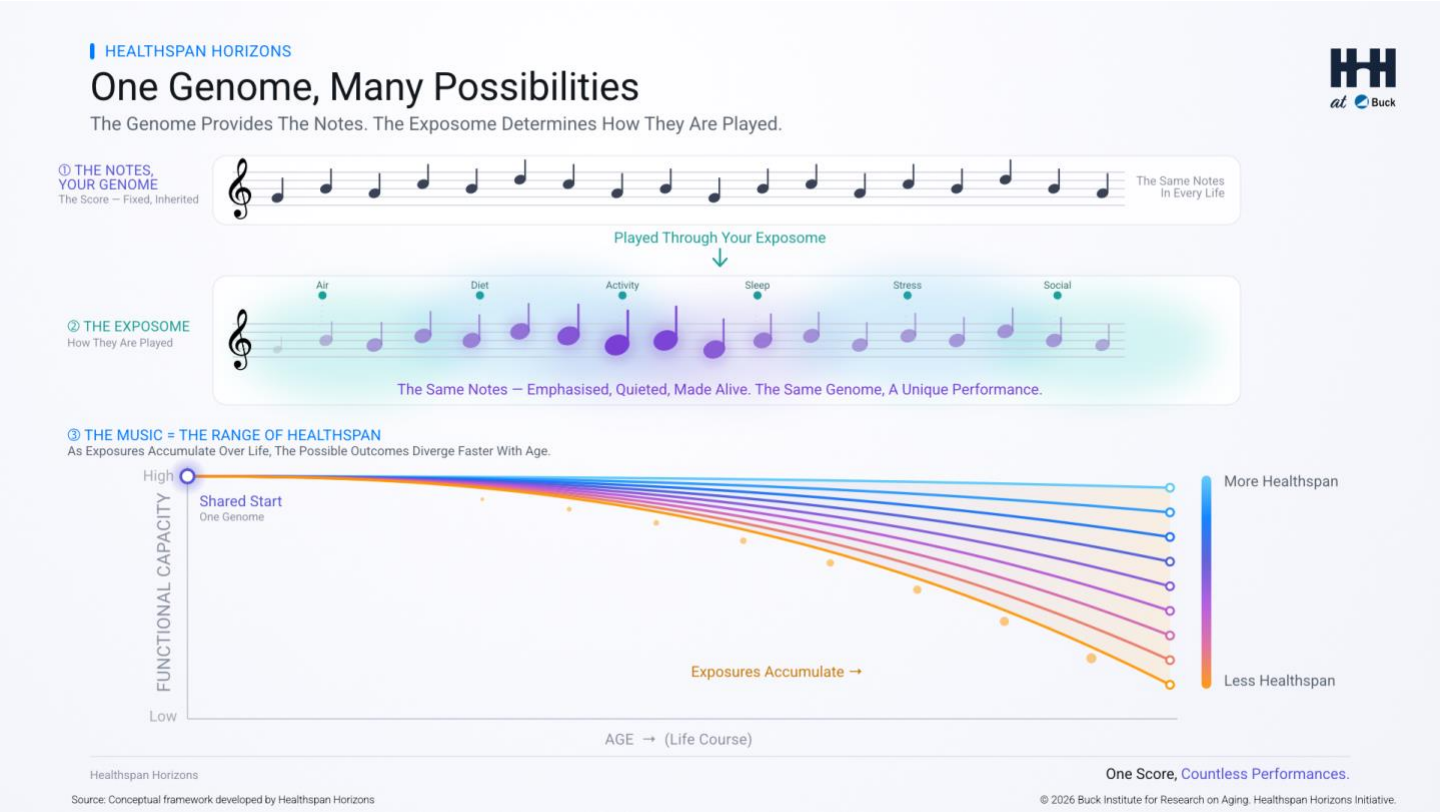
In this paper we will explore how the exposome — the totality of our lifelong environmental exposures — is the missing layer of precision health. Genomics explains predisposition. Clinical biomarkers detect breakdown. Wearables track behavior. The exposome explains the environmental forces acting upon the system that shape our health trajectory. Together, these layers form what we call the Healthspan Data Stack — the integrated view required to understand not only where health stands today, but where it is heading.

> THE CORE IDEA
>
> **The genome explains what is possible. The exposome determines what is actually happening — and what comes next.**

A musical analogy captures this well. The genome is the score sheet — it says which notes can be played. But it is the exposome that determines how the music of our lives actually sounds: which notes (genetic risks) are played loudest and which are muted entirely, the tempo at which we age, and the way the whole performance changes from one moment to the next. As anyone who has heard a cover band can attest, the same song can be interpreted in wildly different ways. By changing our exposome — removing or intervening on harmful exposures and adding beneficial ones — we can choose to march to a different beat, extending healthspan and improving wellness.

FIGURE 1

One Genome, Many Possibilities



The genome provides the notes, but the exposome determines how they are played. Individuals may begin with similar genetic potential, yet differences in environmental, behavioral, and social exposures accumulate over time to produce diverging healthspan trajectories. The same genome can support very different outcomes depending on the environments in which it is expressed.

The genome and the exposome differ profoundly in character. The genome is static, built from four complementary bases arranged in a long but structured sequence. The exposome is dynamic, changing moment by moment, composed of millions of chemicals, microorganisms, and physical and social interactions occurring simultaneously with minimal overarching structure. Capturing the exposome demands deeply phenotyped, longitudinal cohorts that place the environment at the center of health. Until recently, this vision was largely impractical. Advances in molecular profiling, wearable technologies, environmental sensing, and artificial intelligence are now making it possible to measure and contextualize the exposome at a scale that was unimaginable even a decade ago. Healthspan Horizons and its associated Healthspan Compass are examples of this new generation of health infrastructure — a privacy-first, AI-enabled approach to integrating exposomics with biological, behavioral, and clinical measures in order to generate actionable insights into health and wellness.

Crucially, environmental exposures rarely announce themselves first as disease. They manifest first as subtle reductions in resilience, recovery, energy regulation, cognition, inflammatory balance, and adaptive capacity, i.e. the early erosion of the systems that maintain wellness. Seen this way, the exposome ties directly into the way we already think about healthspan — as a determining factor of healthspan trajectories that can be bent towards decline or sustained vitality.

The remainder of this paper develops that argument. We first situate the exposome within precision health and scientific wellness (Hood & Price, 2023). We then show how environmental exposures act as multi-system drivers of healthspan (Section 2). We then examine why the exposome is fundamentally a computational problem — one uniquely suited to modern AI systems — before exploring how environmental exposures can be measured, contextualized, and acted upon through personalized interventions. We close by considering mixtures and the life course, and by affirming that environmental resilience is modifiable to drive home that the exposome is a story of agency, not fatalism.

1.1 The exposome as the missing layer of precision health

Decades of research have shown that health is greatly shaped by the environments we are exposed to. Yet modern medicine largely fails to account for all but the most extreme exposures, and when exposures are considered, they are framed in the context of the cause for a disease that is already manifesting, rather than preventative measures for improving wellness and extending healthspan. Part of the explanation lies in a healthcare system built around diagnosing and treating disease rather than measuring and optimizing wellness. But part is simply the recency of concepts like the exposome, which put into context how the mixture of environmental exposures we experience over the life course impacts health.

The exposome was first defined by Christopher Wild in 2005 as “life-course environmental exposures (including lifestyle factors), from the prenatal period onwards.” (Wild, 2005) In 2024, a diverse group of researchers met at Cold Spring Harbor Laboratory to debate and develop an updated, operational definition. The resulting Banbury Exposomics Consortium put forward that the exposome is the “integrated complication of all physical, chemical, biological, and (psycho)social influences that ‘impact biology’.” (Miller & Banbury Exposomics Consortium, 2025) These definitions highlight the expansiveness of the exposome, its foundational role in health, and its essential position next to the genome in determining healthspan.

Here we focus on the exposome within precision health and scientific wellness, with the goal of using it to extend healthspan and improve wellness. Precision medicine is a movement from broad, generally applied risks toward a personalized understanding of individual-level risks and treatments. It is complemented by a precision environmental health that focuses on the exposome at the level of the individual to improve health and is key to achieving the goals of precision medicine (P. Zhang et al., 2021).

1.2 Using AI and the exposome to improve healthspan

The exposome is vast. It encompasses multiple exposure domains, influences health through diverse biological pathways, and changes continuously throughout life. Understanding it requires more than tracking individual exposures — it requires interpreting them within a broader biological and environmental context. This task is simply infeasible for an individual.

Responsibly designed AI tools such as Healthspan Compass can be the essential bridge between vast exposomics data and meaningful health insights. AI excels at integrating large, heterogeneous data streams and identifying patterns that would be difficult for individuals — or even clinicians — to recognize unaided. With proper context and strong guardrails, AI agents can integrate exposomics from diverse technologies (metabolomics, wearables, remote sensing, soil and water measurements) with health measures; retain the known causal effects of environmental hazards; and continuously monitor for locale-specific hazards such as poor-air-quality days or boil-water advisories.

Within an integrated system such as Healthspan Compass, these agents would be aware of an individual's genetic susceptibilities and current health status, using that context to tailor environmental alerts and recommend validated interventions to improve resilience and optimize healthspan. Importantly this system is not focused on providing single snapshots of data but instead maps healthspan trajectories. Tracking a trajectory is a substantial improvement over the one-time snapshots most individuals receive of their health but requires carefully constructed computational infrastructure to track, contextualize, and report back. The goal is to make this infrastructure accessible to every individual. In this way, Healthspan Compass serves as the integration layer that transforms complex health data into actionable insights.

The Healthspan Data Stack can be visualized as the layers of data that make up an individual and lead to opportunities to optimize their healthspan. At its simplest, the Healthspan Data Stack answers three questions: What is possible? What is happening? And where is health likely headed next? This data stack is composed of the foundational layers of the genome and exposome. The genome establishes predispositions. The exposome shapes how, when, and to what extent those predispositions are expressed. Above these foundational layers sit molecular measurements, wearables, clinical biomarkers, and electronic health records — signals that capture both exposures and biological responses.

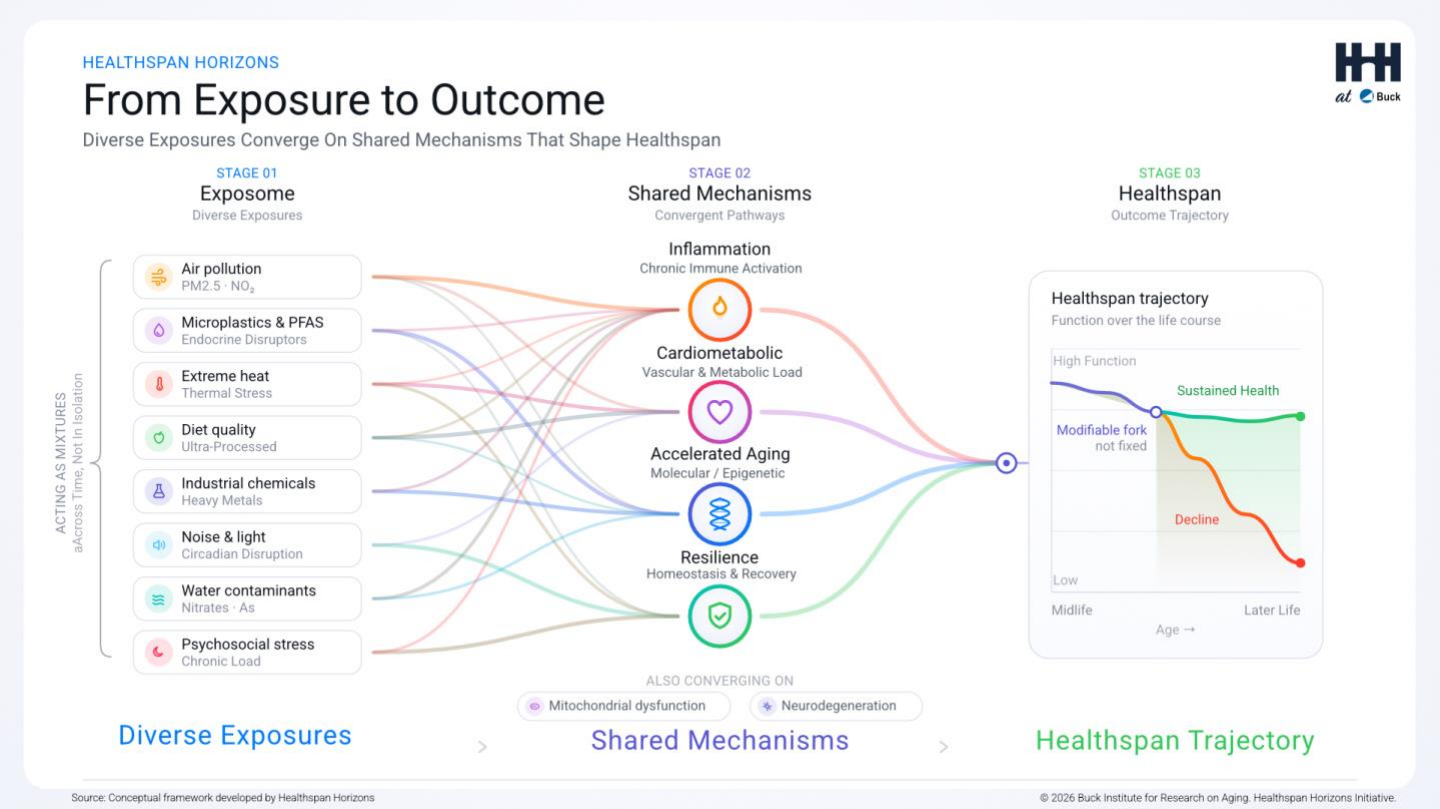
Although the importance of the exposome is increasingly recognized, few systems today continuously integrate environmental exposures with biological and clinical measures at the level of the individual. Healthspan Compass proposes to be such a system, built on the longitudinal data collected in Healthspan Horizons — empowering a new paradigm in which individuals can track, contextualize, and intervene on their personal exposomes.

SECTION 02 · HEALTHSPAN HORIZONS

Environmental Exposures as Healthspan Drivers

FIGURE 2

From Exposure to Outcome: Shared Mechanisms Linking the Exposome to Healthspan



Diverse environmental exposures converge on a smaller number of biological pathways that shape healthspan. Shared mechanisms — including inflammation, cardiometabolic dysfunction, accelerated aging, and resilience — help explain how many different exposures ultimately influence long-term health outcomes.

Environmental exposures may appear diverse, but many converge on a relatively small set of biological mechanisms, including inflammation, accelerated aging, mitochondrial dysfunction, neurodegeneration, and impaired recovery and resilience (Peters et al., 2021). Viewing the exposome through these shared mechanisms provides a practical framework for understanding how environmental exposures influence healthspan and the body's ability to adapt to continual stressors.

In the sections that follow we explore the impacts of the exposome on health organized around four key mechanistic domains: inflammation, cardiometabolic effects, accelerated aging, and resilience/homeostasis. Within each domain we discuss the major environmental contributors. Like individual genes and genetic variants in the genome, exposures have historically been studied in isolation. While this approach has generated invaluable insights, it misses an important reality: exposures occur simultaneously and interact with

one another. Throughout this section we discuss individual exposures, while recognizing that real-world health outcomes emerge from combinations of exposures acting across time. We return to this concept of mixtures later in the paper.

Inflammation: The Common Proximal Response

Across a wide range of environmental exposures, inflammation emerges as one of the most common biological pathways linking the exposome to healthspan. Inflammation (and the closely related oxidative stress) serves as a shared entry point through which air pollution, heat, and many chemical exposures begin to affect the body. Reactive oxygen species are generated under normal physiology and held in check by antioxidant defenses — chief among them the NRF2 transcription factor, which governs xenobiotic metabolism, glutathione synthesis, DNA repair, and mitochondrial physiology. When environmental insults overwhelm these defenses, the balance tips toward inflammation, cell death, and organ damage (Peters et al., 2021).

Fine particulate matter (PM2.5) and ozone are perhaps the two clearest example exposure, inflammation, and health effects. These particles are small enough to penetrate airway defenses and even diffuse out of the lung, generating oxidative stress and a systemic inflammatory response that radiates well beyond the respiratory tract (Brook et al., 2010; U.S. Environmental Protection Agency, 2019; World Health Organization. Regional Office for Europe, 2021). Ozone is so reactive that it never leaves the lungs, but due to the systemic inflammation triggered by airway inflammation and endothelial cell disruption, ozone exposure is not only associated with lung damage but can have systemic effects (U.S. Environmental Protection Agency, 2020; World Health Organization. Regional Office for Europe, 2021). Similar inflammatory pathways have also been observed for nitrogen dioxide (NO_2) and volatile organic compounds, which contribute to respiratory and systemic health effects (Kasdagli et al., 2024; N. Liu et al., 2022; Riggs et al., 2022; U.S. Environmental Protection Agency, 2016).

Inflammation is also a key mechanism for exposures other than air. Extreme heat raises inflammation and oxidative stress as part of a broader stress response that includes cardiovascular strain, impaired thermoregulation, and dehydration (Xu et al., 2025). PFAS are a ubiquitous exposure with a long half-life leading them to be known as forever chemicals. Associated with water contamination as well as consumer products, inflammation is one of the key pathways linked with PFAS exposure and resulting health effects (Fenton et al., 2021; India-Aldana et al., 2023). Microplastics are an increasingly studied exposure and while studies of human health effects are limited animal models and in vitro studies have implicated microplastics in oxidative stress and inflammation, alongside neurotoxicity, and metabolic disruption (Prata et al., 2020;

Vethaak & Legler, 2021). Importantly, the exposome is not solely a source of risk. Beneficial exposures — including diets rich in diverse antioxidant-containing foods — can help counterbalance environmental stressors and support resilience (Thangaraj et al., 2026; Z. Zhang et al., 2025).

Cardiometabolic Effects

Once inflammation becomes systemic, two of its most consequential targets are the cardiovascular and metabolic systems. Endocrine disruption compounds the damage by interfering with the hormonal regulation of metabolism, while altered intercellular communication propagates dysfunction between tissues (Peters et al., 2021). Cardiometabolic health provides one of the clearest examples of how environmental exposures translate into measurable changes in healthspan, influencing not only disease risk but also energy, functional capacity, and resilience over time.

Air pollution is, again, the most thoroughly documented cardiometabolic stressor among the exposome domains. Both the US EPA and the World Health Organization have judged PM2.5 a causal contributor to cardiovascular disease and mortality, and its associated burden spans hospital admissions, cardiovascular and renal disease, and increased frailty (Ab Manan et al., 2018; Li et al., 2025; U.S. Environmental Protection Agency, 2019; World Health Organization. Regional Office for Europe, 2021). Poor air quality is responsible for up to 200,000 deaths each year in the United States (Burnett et al., 2018; Caiazzo et al., 2013), and the Global Burden of Disease study ranked ambient particulate matter the seventh-highest risk factor for disability-adjusted life years (a population-level measure that captures years of healthy life lost), which was a higher ranking than alcohol usage (Murray et al., 2020). Gaseous pollutants contribute their own cardiovascular signal, with evidence linking ozone and NO2 to cardiovascular effects in addition to their respiratory toll (Donzelli & Suarez-Varela, 2024; Kasdagli et al., 2024).

Other domains feed the same cardiometabolic endpoints. Heavy metals act across the life course through organ-specific injury, including the renal, oncogenic, and cardiovascular effects of exposure in adulthood (Pant et al., 2024). PFAS are considered a causal factor in dyslipidemia and there is growing evidence linking them with cardiovascular disease and metabolic syndrome (National Academies of Sciences et al., 2022), and endocrine-disrupting chemicals more broadly are linked to a host metabolic effects across the life course (Haverinen et al., 2021; Yilmaz et al., 2020). Extreme heat has a chronic cardiometabolic burden and triggers acute cardiovascular events such as strokes, heart attacks, and cardiovascular and pulmonary mortality (Delaney et al., 2025; J. Liu et al., 2024). The behavioral exposome modulates all of this in both positive and negative ways. On the positive side, dietary shifts can add up to ten years of life expectancy (Fadnes et al., 2023) and regular exercise three to four years (Moore et al., 2012). On the negative side cigarette smoking and

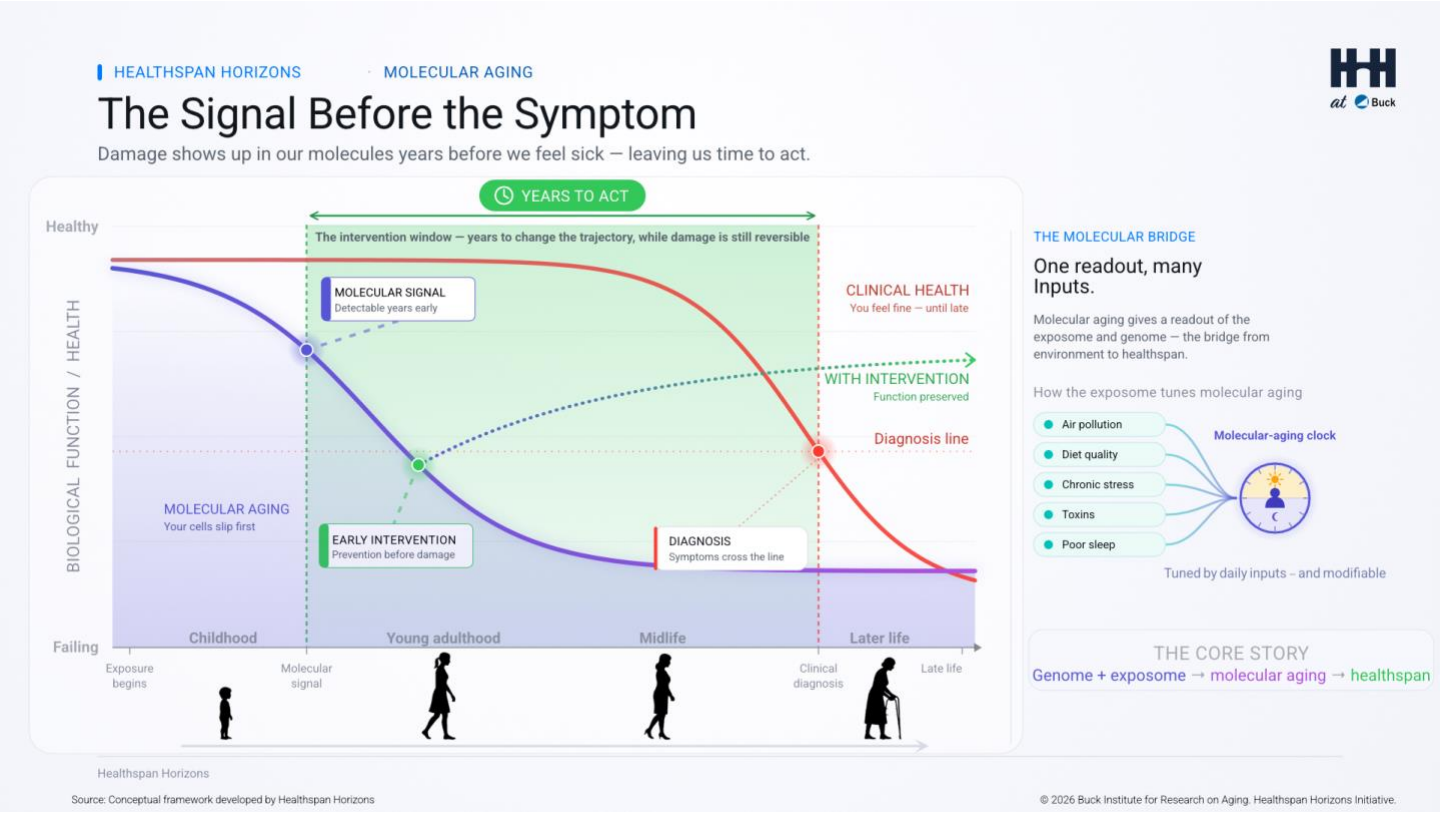
sedentary lifestyle are associated with cardiometabolic decline (Edwardson et al., 2012; Pasupathi et al., 2009), and vaping is brining novel cardiometabolic risks from flavorings and metal emissions (Kundu et al., 2025; Reynolds et al., 2024).

Together, these examples illustrate that the exposome is not merely something that happens to us — it is also shaped by many of the choices we make every day.

Molecular Aging

FIGURE 3

The Signal Before the Symptom: Molecular Aging as an Early Indicator of Healthspan



Environmental exposures leave measurable biological signatures long before clinical symptoms emerge. Molecular aging biomarkers provide an early readout of cumulative environmental and biological stress, creating opportunities for earlier intervention and more proactive healthspan management.

In addition to these traditional clinical endpoints, environmental exposures leave a signature at the molecular level, often years before any diagnosis. These biological signals often emerge years before disease becomes clinically apparent, offering an opportunity to detect shifts in health trajectory while intervention is still possible

(Rappaport et al., 2026). Molecular aging is a key biological indicator to capture for understanding healthspan as it can be a summary readout of many underlying factors which is helpful when attempting to make sense of something as expansive as the exposome. Environmental exposures appear to act jointly on a telomere–mitochondrial aging axis, altering mitochondrial DNA content and nucleus–mitochondria crosstalk, and they can trigger the senescence-associated secretory phenotype through which aging cells broadcast inflammatory signals to their neighbors (Peters et al., 2021) and are associated with a range of molecular aging biomarkers (Dhingra et al., 2018; Oblak et al., 2021). Molecular aging biomarkers may serve as an important bridge between environmental exposures and healthspan outcomes because they integrate signals from many exposures into a single, interpretable measure.

Air pollution is the best-characterized environmental exposure related to aging. Its effects begin at the subclinical level and appear in DNA methylation, accelerated epigenetic aging, altered gene expression, and shifts in the proteome and metabolome (Dhingra et al., 2018; Peters et al., 2021; Ward-Caviness et al., 2016). Extreme heat shows the same pattern: heat exposure has been associated with accelerated aging measured by molecular biomarkers (Chiu et al., 2024; Choi & Ailshire, 2025), underscoring that its effects persist at the molecular level long after the temperature falls. Heavy metals have also been associated with accelerated aging (Ryoo et al., 2025), while there is growing evidence that positive behavioral factors like a balanced diet and regular exercise can slow, or possibly even reverse, the trajectory of molecular aging biomarkers (Fitzgerald et al., 2021; Kawamura et al., 2025; Quach et al., 2017).

Resilience: Cumulative Burden and the Erosion of Homeostasis

Resilience — the body's ability to maintain or regain homeostasis in the face of environmental stressors — may be one of the most important determinants of long-term healthspan. Being able to “return to baseline” after an external shock such as a heat wave, or even in the face of continual exposures to PFAS, air pollution, and endocrine disrupting chemicals is likely a key determining factor in which stressors produced a sustained impact on aging and healthspan and which are effectively managed by the body with no long-term impact.

Viewing the exposome through the lens of resilience highlights three important features that help explain how environmental exposures shape healthspan over time. The first is cumulative effect: while short-term spikes in exposure can be consequential it is the cumulative effects of exposures that are most strongly associated with significant biological alterations and clinical events (Beverland et al., 2012; Panni et al., 2016). This can be biologically captured through the “seed and soil” model where long-term exposures combine with existing genomics to represent the soil that can be a fertile ground for negative health outcomes to sprout from. The seeds in this model are short-term stressors (or cellular signals resulting from stressors) whose impacts are

determined based on the type of soil they land within (Bowers & McCullough, 2017). In this manner we can see how it's not just the immediate stressor, but also the current physiologic state determined by long-term exposures and resilience that results in health effects.

The second feature is engagement of the body's central stress systems. Environmental exposures are processed as systemic stressors, activating the hypothalamic–pituitary–adrenal (HPA) axis and the broader neuroendocrine stress response, in which exposures modulate the nervous system through sensory organs and downstream stress responses (Peters et al., 2021). Air pollution, for instance, links peripheral insult to central nervous system effects through precisely this stress-axis activation and its contribution to allostatic load (Thomson, 2019). The same is true for a wide variety of exposures such as heavy metals, PFAS, and phthalates — they can all trigger systemic disruptions through dysregulation of endocrine signaling and pathways like the HPA axis (Bashir & Obeng-Gyasi, 2022; Pande et al., 2024; Rana, 2014; Sears et al., 2024).

The third feature follows from the first two: the steady degradation of homeostasis. As environmental stressors accumulate and repeatedly engage these stress systems, the regulatory networks that maintain stability — cardiovascular, inflammatory, renal, metabolic, and neuroendocrine — are forced to operate ever further from their optimal set points. This can be represented by concepts like allostatic load (Beckie, 2012), where an increasing allostatic load reflects the cumulative wear of repeated adaptation and resulting drift from optimal set points. As in the aforementioned seed and soil model, it is this elevated allostatic load that can convert chronic, low-grade exposure into acute, discrete events: a system already operating near its limits is tipped over by a hot day, a pollution episode, or an infection, producing the heart attacks, strokes, and hospitalizations that mark health consequences observed once resilience is exceeded.

This is also where the modifiability of resilience becomes clear. Adaptive capacity is not fixed, nor is it purely determined by internal biological factors. Communities with lower area-level adaptive capacity — fewer cooling resources, higher chronic disease burden, greater socioeconomic disadvantage — suffer greater heat-related health effects (Tsai et al., 2026), and adaptive capacity is precisely the kind of system-level resilience that healthspan-oriented intervention can target at both individual and policy levels. The resilience lens gives an alternate way of approaching the exposome: the goal is not simply to reduce environmental exposures, but to strengthen the systems that allow individuals to remain resilient when exposures inevitably occur.

Environmental Sensitivity and Exposure Inequities

As we mentioned earlier in this section, environmental exposures interact with genetics and existing health status to manifest health outcomes. This is immediately obvious when we consider that not all individuals respond equally to environmental exposures. Age and chronic disease are the most recognized sensitivity

factors (Peled, 2011). The best-known genetic sensitivity factors are related to detoxification (e.g. GSTM1) and disease-related variants (Hollman et al., 2016; Simonds et al., 2016; Ward-Caviness, 2019). Research on polygenic risk scores is likely to surface some of the first polygenic exposure-sensitivity scores as exposure sensitivity is quantified.

Epigenetic age has recently emerged as a modifiable sensitivity factor. Population studies and controlled human exposure studies alike suggest that accelerated epigenetic age heightens the response to air pollution (Jackson et al., 2025; Ward-Caviness et al., 2020; Weston et al., 2024). Because molecular aging biomarkers are potentially modifiable (Fitzgerald et al., 2021; Kawamura et al., 2025; Quach et al., 2017), they offer a way to understand — and act on — environmental sensitivity that age and genetic variation do not. This fits modern views of resilience, which frame health as the capacity to withstand stressors that would otherwise tip a person from homeostasis toward functional decline and chronic disease. Future measures of resilience may double as reversible measures of environmental sensitivity — a direct, actionable bridge to optimizing healthspan.

Environmental risks are not distributed equally across populations. Racial and ethnic minorities and lower-income communities face higher air pollution and greater pollution-related mortality (Jbaily et al., 2022). Consumer-product use drives greater exposure to toxic chemicals among Black women and among younger and middle-aged adults (Barrett et al., 2025), partly through racialized beauty norms that encourage use of toxin-laden products (Edwards et al., 2023). “Cancer Alley,” an 85-mile stretch along the Mississippi River in Louisiana dense with petrochemical industry, exemplifies these injustices as this historically African-American and lower income corridor features extremely high cancer rates often linked with the concentration of the petrochemical industry there (Singer, 2011).

SECTION 03 · HEALTHSPAN HORIZONS

From Healthspan Optimization to Resilience Mapping: A Computational Challenge

The challenge before us is no longer whether environmental exposures matter. The evidence on that is settled. The challenge is computational.

The exposome is too multidimensional for any individual — even an environmental expert or clinician — to track unaided. It requires longitudinal interpretation across hundreds of thousands of simultaneous, shifting inputs, and it demands that those inputs be connected to subtle, early changes in resilience, recovery, and functional decline rather than to disease alone. This is exactly the kind of problem at which artificial intelligence excels, and it is what makes AI not an aspirational add-on to environmental health but a necessary foundation of it. Framing the exposome this way — as a computational and longitudinal interpretation problem — is what moves us from detecting disease after the fact toward mapping resilience before it erodes. The challenge is understanding, measuring, and acting on them at the scale and complexity at which they occur in real life. This is fundamentally a computational problem. The exposome is too multidimensional, dynamic, and individualized for any person — or clinician — to interpret unaided. Turning environmental data into actionable healthspan insights therefore requires systems capable of integrating exposures, biology, and time simultaneously.

3.1 Measuring the Exposome

Measuring the exposome draws on a range of technologies, many of which will be deployed in Healthspan Horizons and integrated into Healthspan Compass. Metabolomics is a foundational technology for measuring the exposome. Modern metabolomics techniques can evaluate over 100,000 chemicals in a tissue (often blood) with high accuracy. Although a tradeoff remains between quantification and discovery, and not every chemical can be profiled, metabolomics is invaluable for exposome-oriented exposure science and for grasping the vast number of chemicals we encounter daily (Walker et al., 2019). Measuring the exposome therefore resembles assembling a mosaic: each technology captures part of the picture, but meaningful interpretation emerges only when those pieces are integrated.

No single technology can capture the exposome. Metabolomics can profile tens of thousands of chemicals simultaneously, while environmental sensors, wearables, biological samples, and surveys each provide complementary views of an individual's exposure landscape. Microplastics are a great example of this as they require several complementary technologies such as Fourier-transform infrared spectroscopy, Raman spectroscopy, and electron microscopy to fully evaluate since no single method can resolve polymer type, size,

composition, shape, and quantity at once. Ambient exposures can be tracked by devices in the home, the neighborhood, or worn on the body, measuring particulate matter, gases, temperature, and humidity to provide a near continuous readout of the environments we move through. Other exposures such as heavy metals, endocrine disrupting chemicals, volatile organic compounds, dioxins, and pesticides all have a wide range of evaluation methodologies that differ based on sample type, limit of detection needs, specificity, and throughput.

Wearables have become invaluable for capturing behaviors like exercise, sleep quality, and even stress responses. Simple adsorbent wristbands (often made of silicone) can sample the ambient chemical exposome which can be quantified via metabolomics, complementing tissue measurements by capturing chemicals before biotransformation. Finally, surveys and self-report remain irreplaceable for diet and many social stressors; even where these are partly reflected in metabolomics or wearables, full understanding often requires the individual's own account, making systems that capture, harmonize, and link such information to outcomes essential to measuring the exposome in order to improve healthspan. The challenge is not simply collecting data. It is integrating diverse measurements, understanding their strengths and limitations, and translating them into meaningful health insights. This is precisely where well-designed AI systems can add value.

3.2 Mixtures and Life Course

Any discussion of the exposome must consider two realities: exposures occur in mixtures, and they occur across time. These two dimensions — mixtures and timing — are what distinguish the exposome from traditional approaches that evaluate one exposure at a time. As the exposome definitions that we laid out at the beginning of the document make clear, the exposome is inherently about not just what exposures occur, but when they occur, and which ones occur together versus at different time periods. We cannot survey all mixtures and timeframes of exposure here, but recent statistical advances have enabled far more mixtures-based and cumulative effect studies, which more accurately reflect the real world experiences of individuals as compared to single exposure studies (Carlin & Rider, 2024). These methodological advances are reshaping environmental health toward a more comprehensive, cumulative understanding. Summary measures that fold multiple environmental aspects into a single interpretable score, such as the climate vulnerability index (Tee Lewis et al., 2023), are increasingly used and often far more powerful than individual exposures.

Just as exposures are not limited to a single compound, they are not limited to a single moment. The developmental origins of health and disease (DOHaD) hypothesis holds that much disease risk is established during development — even for adult-onset conditions — meaning that early-life exposures can carry lifelong consequences (Grandjean et al., 2015). The Dutch Famine study, perhaps the most widely recognized example

of early-life and transgenerational effects, demonstrated how exposures during critical developmental windows in parents (particularly fathers) influenced health outcomes in their children (Veenendaal et al., 2013).

Systems for tracking the exposome must therefore account for both critical windows of exposure and cumulative burden across the life course. This dramatically increases complexity. Understanding healthspan requires knowing not only what exposures occurred, but also when they occurred, in what combinations, and within what biological context. As measurements become more frequent and comprehensive, patterns emerge that reflect not only the accumulation of exposures over time, but also the timing of those exposures relative to key stages of development, aging, and resilience.

Capturing, indexing, and interpreting these multidimensional relationships is one of the central challenges of exposomics — and one of the reasons the exposome has become such a compelling application for AI-enabled analysis.

SECTION 04 · HEALTHSPAN HORIZONS

Acting on the Exposome: Interventions and AI

Measurement is most valuable when it leads to action. Interventions against environmental exposures take several forms, and AI is the connective tissue that turns measurement into personalized, validated action. Environmental health has often focused on identifying hazards. A healthspan perspective adds a second question: what can individuals do about them? The answer lies in a combination of exposure reduction, resilience building, and personalized decision support.

Policy change remains the primary intervention against widespread exposures with well-established health effects. But policy is slow and, as noted, blind to individual biology and circumstance. For that, more personal interventions are needed, coupled with AI systems that can understand individual risks and sensitivities, recommend validated interventions, and track their effectiveness at individual and population scales.

One of the strongest recurring findings in environmental health is that healthier individuals are generally more resilient to environmental stressors. This suggests that improving healthspan may itself be a powerful environmental intervention. The benefits likely extend beyond reducing disease risk to improving resilience and wellness even among otherwise healthy individuals. A 2024 study of young, fit volunteers undergoing controlled ozone exposure found that those with a lower epigenetic age experienced smaller cardiovascular changes despite exercising throughout the two-hour experiment (Weston et al., 2024). Improved wellness, in other words, can confer environmental resilience even in the already healthy — a strong argument that resilience is modifiable and worth building, since not every exposure can be avoided.

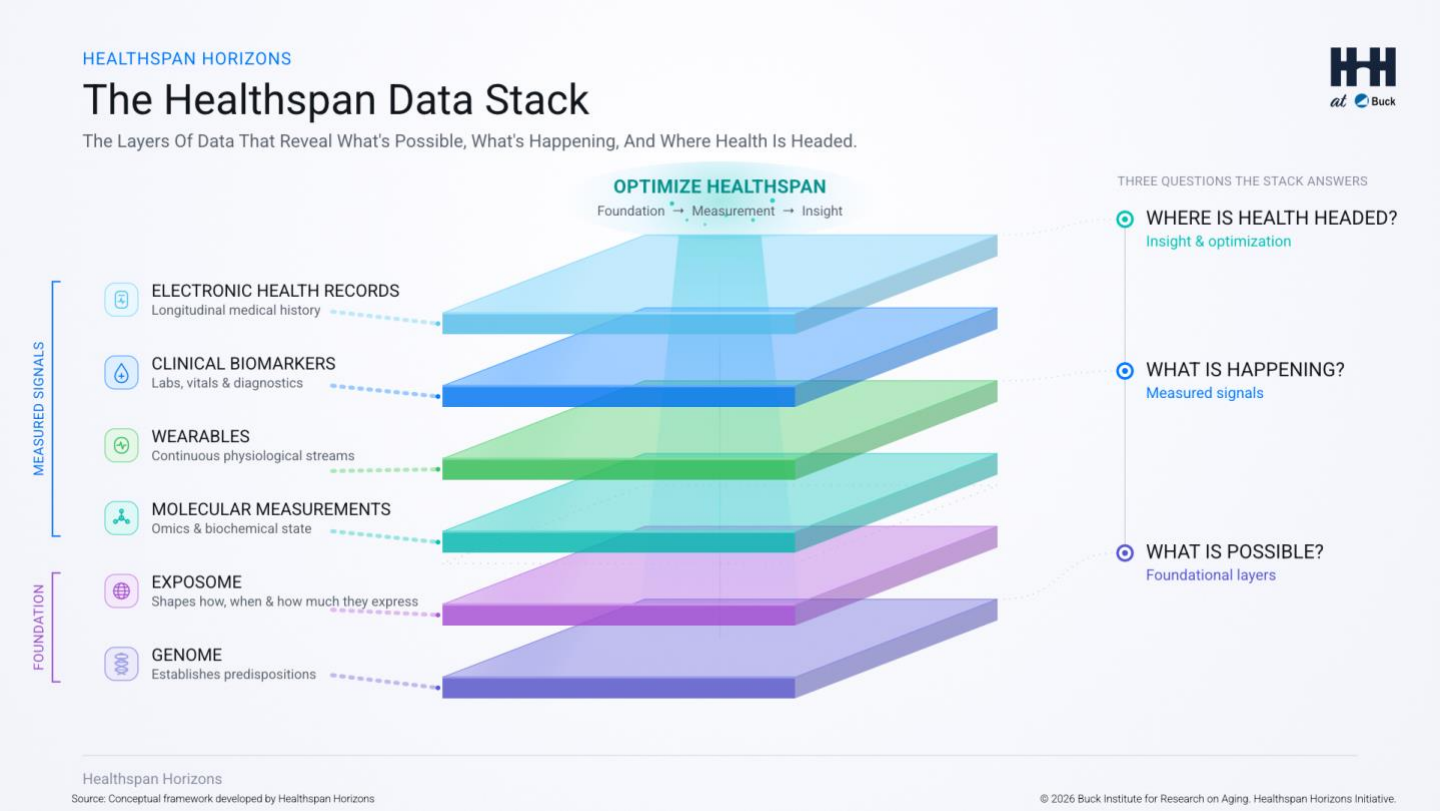
Diet is another common intervention. Fish oil and vitamins C, E, and B12 (Chen et al., 2022; Ilaghi et al., 2024; Laumbach et al., 2015) attenuate air-pollution effects, and antioxidant-rich foods and dietary diversity may offer some protection against exposures such as PFAS (Thangaraj et al., 2026; Z. Zhang et al., 2025). Removing the hazard is equally important: well-fitted respirators for air pollution, in-home air and water filters — especially when paired with monitoring to confirm performance — and staying indoors during poor air quality or extreme heat. When air conditioning or adequate ventilation is unavailable during extreme heat, seeking out a nearby cooling station is an effective fallback. The future of environmental health is therefore not simply avoiding risk. It is understanding which exposures matter most for a given individual, identifying which interventions are most likely to help, and continuously learning from outcomes. In this model, environmental health becomes personalized, adaptive, and proactive rather than reactive. This is where AI-assisted systems may ultimately have their greatest impact.

SECTION 05 · HEALTHSPAN HORIZONS

Toward Personalized Environmental Health & Resilience

FIGURE 4

The Healthspan Data Stack: Integrating the Genome, Exposome, and Measured Signals



A comprehensive understanding of healthspan requires integrating multiple layers of information. The genome and exposome form the foundational layers, while molecular measurements, wearables, clinical biomarkers, and electronic health records provide longitudinal signals of biological state and function. Together, these layers help answer three central questions: What is possible? What is happening? And where is health headed?

What might a fully realized environmental health system look like?

Moving toward a personalized view of environmental health requires the same focused, data-driven approach that has transformed precision medicine. Revolutions in genomics, clinical informatics, and biomarker development have ushered in increasingly precise care, yet the environment has remained a critical missing layer. The exposome is multidimensional, constantly changing, and inherently difficult to measure. At the same time, the randomized controlled trial — the traditional gold standard of medical evidence — is often poorly suited, for both practical and ethical reasons, to studying the complexity of environmental exposures. Together, these challenges have limited the incorporation of environmental data into routine healthcare. As a

result, few physicians discuss environmental risks with patients, even though most recognize the environment as an important determinant of health (Massachusetts Department of Public Health, 2021). Individuals, too, want to incorporate environmental factors into their health decisions but face barriers including limited access to environmentally informed care, financial constraints, weak policy guidance, and a shortage of trusted information (McCabe et al., 2025).

Closing these gaps is where AI becomes decisive. The exposome only becomes interpretable — and therefore actionable — when its immense complexity can be understood within the context of an individual's biology, health status, and lived environment.

Viewed through this lens, environmental health begins to look fundamentally different. Rather than a world in which “everything is toxic” and individuals are left waiting for regulators to intervene, people gain the ability to understand and manage their own environmental risks. Exposures can be tracked and contextualized alongside genomic information, clinical biomarkers, wearable data, and other health measures to identify which environmental factors are most likely to influence health today and in the future. Fatalism is replaced by agency.

AGENCY, NOT FATALISM

The exposome is a story about agency, not fate — health is no longer a static snapshot, but a continuously evolving trajectory that can be measured, understood, and influenced.

In this model, health is no longer viewed as a static snapshot or simply the absence of disease. Instead, it becomes a continuously evolving trajectory that can be measured, understood, and influenced. As interventions are implemented, their effects on environmental resilience — the ability to maintain homeostasis in the face of stressors — can also be monitored, creating opportunities for continuous learning and adaptation.

Importantly, this approach is not limited to highly sensitive individuals. Real-time information about air quality, extreme heat, water quality, and other environmental factors is already widely available and increasingly predictable. While a person with asthma avoiding outdoor exercise on a high-ozone day may be an obvious example, environmental exposures affect everyone. We have already seen evidence that even young, healthy individuals differ in their responses to environmental stressors, and that some of these differences are

reflected in measurable molecular biomarkers. Moreover, environmental exposures accumulate over time, gradually altering resilience and shaping how future stressors are experienced.

Managing this complexity requires privacy-first, validated systems capable of integrating environmental, biological, and behavioral data into actionable insights. Pairing technologies such as Healthspan Compass with longitudinal initiatives like Healthspan Horizons creates an opportunity to incorporate the exposome into the broader Healthspan Data Stack alongside genomics, clinical biomarkers, wearables, and lifestyle data. Integrating these layers moves us toward a new paradigm of healthspan optimization — one that recognizes that health emerges from the interaction between the genome and the exposome, not from either in isolation.

The tools needed to build this future are emerging rapidly, though careful validation and governance will be essential to ensure they remain trustworthy and scientifically robust. As Healthspan Horizons launches, it aims to provide a foundational layer of data and infrastructure that enables individuals to better understand their exposures, contextualize their health trajectories, and take informed action to improve long-term wellness.

The exposome reminds us that health is shaped not only by what is written in our genomes, but also by the environments we create, inhabit, and adapt to throughout our lives. Understanding those interactions may be one of the most important opportunities for extending healthspan in the decades ahead.

References

01 Ab Manan, N., Aizuddin, A. N., & Hod, R. (2018). Effect of Air Pollution and Hospital Admission: A Systematic Review. Annals of Global Health, 84(4), 670–678. https://doi.org/10.29024/aogh.2376

02 Barrett, E. S., Wadie, K., Getz, K., Greenberg, P., Moore, T., & Llanos, A. A. M. (2025). Evaluating personal care product use by Environmental Working Group hazard scores in relation to consumers' sociodemographic characteristics, purchasing behaviors, and product safety perceptions. Journal of Exposure Science & Environmental Epidemiology, 35(6), 921–932. https://doi.org/10.1038/s41370-025-00751-9

03 Bashir, T., & Obeng-Gyasi, E. (2022). The Association between Multiple Per- and Polyfluoroalkyl Substances' Serum Levels and Allostatic Load. International Journal of Environmental Research and Public Health, 19(9), 5455. https://doi.org/10.3390/ijerph19095455

04 Beckie, T. M. (2012). A Systematic Review of Allostatic Load, Health, and Health Disparities. Biological Research For Nursing, 14(4), 311–346. https://doi.org/10.1177/1099800412455688

05 Beverland, I. J., Cohen, G. R., Heal, M. R., Carder, M., Yap, C., Robertson, C., Hart, C. L., & Agius, R. M. (2012). A Comparison of Short-term and Long-term Air Pollution Exposure Associations with Mortality in Two Cohorts in Scotland. Environmental Health Perspectives, 120(9), 1280–1285. https://doi.org/10.1289/ehp.1104509

06 Bowers, E. C., & McCullough, S. D. (2017). Linking the Epigenome with Exposure Effects and Susceptibility: The Epigenetic Seed and Soil Model. Toxicological Sciences, 155(2), 302–314. https://doi.org/10.1093/toxsci/kfw215

07 Brook, R. D., Rajagopalan, S., Pope, C. A., Brook, J. R., Bhatnagar, A., Diez-Roux, A. V., Holguin, F., Hong, Y., Luepker, R. V., Mittleman, M. A., Peters, A., Siscovick, D., Smith, S. C., Whitsel, L., & Kaufman, J. D. (2010). Particulate Matter Air Pollution and Cardiovascular Disease. Circulation, 121(21), 2331–2378. https://doi.org/10.1161/CIR.0b013e3181dbece1

08 Burnett, R., Chen, H., Szyszkowicz, M., Fann, N., Hubbell, B., Pope, C. A., Apte, J. S., Brauer, M., Cohen, A., Weichenthal, S., Coggins, J., Di, Q., Brunekreef, B., Frostad, J., Lim, S. S., Kan, H., Walker, K. D., Thurston, G. D., Hayes, R. B., … Spadaro, J. V. (2018). Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proceedings of the National Academy of Sciences, 115(38), 9592–9597. https://doi.org/10.1073/pnas.1803222115

09 Caiazzo, F., Ashok, A., Waitz, I. A., Yim, S. H. L., & Barrett, S. R. H. (2013). Air pollution and early deaths in the United States. Part I: Quantifying the impact of major sectors in 2005. Atmospheric Environment, 79, 198–208. https://doi.org/10.1016/j.atmosenv.2013.05.081

10 Carlin, D. J., & Rider, C. V. (2024). Combined Exposures and Mixtures Research: An Enduring NIEHS Priority. Environmental Health Perspectives, 132(7), 075001. https://doi.org/10.1289/EHP14340

11 Chen, H., Tong, H., Shen, W., Montilla, T. S., Case, M. W., Almond, M. A., Wells, H. B., Alexis, N. E., Peden, D. B., Rappold, A. G., Diaz-Sanchez, D., Devlin, R. B., Bromberg, P. A., & Samet, J. M. (2022). Fish oil blunts lung function decrements induced by acute exposure to ozone in young healthy adults: A randomized trial. Environment International, 167, 107407. https://doi.org/10.1016/j.envint.2022.107407

12 Chiu, K.-C., Hsieh, M.-S., Huang, Y.-T., & Liu, C.-Y. (2024). Exposure to ambient temperature and heat index in relation to DNA methylation age: A population-based study in Taiwan. Environment International, 186, 108581. https://doi.org/10.1016/j.envint.2024.108581

13 Choi, E. Y., & Ailshire, J. A. (2025). Ambient outdoor heat and accelerated epigenetic aging among older adults in the US. Science Advances, 11(9), eadr0616. https://doi.org/10.1126/sciadv.adr0616

14 Delaney, S. W., Stegmuller, A., Mork, D., Mock, L., Bell, M. L., Gill, T. M., Braun, D., & Zanobetti, A. (2025). Extreme Heat and Hospitalization Among Older Persons With Alzheimer Disease and Related Dementias. JAMA Internal Medicine, 185(4), 412–421. https://doi.org/10.1001/jamainternmed.2024.7719

15 Dhingra, R., Nwanaji-Enwerem, J. C., Samet, M., & Ward-Caviness, C. K. (2018). DNA Methylation Age—Environmental Influences, Health Impacts, and Its Role in Environmental Epidemiology. Current Environmental Health Reports, 5(3), 317–327. https://doi.org/10.1007/s40572-018-0203-2

16 Donzelli, G., & Suarez-Varela, M. M. (2024). Tropospheric Ozone: A Critical Review of the Literature on Emissions, Exposure, and Health Effects. Atmosphere, 15(7). https://doi.org/10.3390/atmos15070779

17 Edwards, L., Ahmed, L., Martinez, L., Huda, S., Shamasunder, B., McDonald, J. A., Dubrow, R., Morton, B., & Zota, A. R. (2023). Beauty Inside Out: Examining Beauty Product Use Among Diverse Women and Femme-Identifying Individuals in Northern Manhattan and South Bronx Through an Environmental Justice Framework. Environmental Justice, 16(6), 449–460. https://doi.org/10.1089/env.2022.0053

18 Edwardson, C. L., Gorely, T., Davies, M. J., Gray, L. J., Khunti, K., Wilmot, E. G., Yates, T., & Biddle, S. J. H. (2012). Association of Sedentary Behaviour with Metabolic Syndrome: A Meta-Analysis. PLOS ONE, 7(4), e34916. https://doi.org/10.1371/journal.pone.0034916

19 Fadnes, L. T., Celis-Morales, C., Økland, J.-M., Parra-Soto, S., Livingstone, K. M., Ho, F. K., Pell, J. P., Balakrishna, R., Javadi Arjmand, E., Johansson, K. A., Haaland, Ø. A., & Mathers, J. C. (2023). Life expectancy can increase by up to 10 years following sustained shifts towards healthier diets in the United Kingdom. Nature Food, 4(11), 961–965. https://doi.org/10.1038/s43016-023-00868-w

20 Fenton, S. E., Ducatman, A., Boobis, A., DeWitt, J. C., Lau, C., Ng, C., Smith, J. S., & Roberts, S. M. (2021). Per- and Polyfluoroalkyl Substance Toxicity and Human Health Review: Current State of Knowledge and Strategies for Informing Future Research. Environmental Toxicology and Chemistry, 40(3), 606–630. https://doi.org/10.1002/etc.4890

21 Fitzgerald, K. N., Hodges, R., Hanes, D., Stack, E., Cheishvili, D., Szyf, M., Henkel, J., Twedt, M. W., Giannopoulou, D., Herdell, J., Logan, S., & Bradley, R. (2021). Potential reversal of epigenetic age using a diet and lifestyle intervention: A pilot randomized clinical trial. Aging (Albany NY), 13(7), 9419–9432. https://doi.org/10.18632/aging.202913

22 Grandjean, P., Barouki, R., Bellinger, D. C., Casteleyn, L., Chadwick, L. H., Cordier, S., Etzel, R. A., Gray, K. A., Ha, E.-H., Junien, C., Karagas, M., Kawamoto, T., Lawrence, B. P., Perera, F. P., Prins, G. S., Puga, A., Rosenfeld, C. S., Sherr, D. H., Sly, P. D., … Heindel, J. J. (2015). Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives. Endocrinology, 156(10), 3408–3415. https://doi.org/10.1210/en.2015-1350

23 Haverinen, E., Fernandez, M. F., Mustieles, V., & Tolonen, H. (2021). Metabolic Syndrome and Endocrine Disrupting Chemicals: An Overview of Exposure and Health Effects. International Journal of Environmental Research and Public Health, 18(24). https://doi.org/10.3390/ijerph182413047

24 Hood, L., & Price, N. D. (2023). The Age of Scientific Wellness. Harvard Business Review Press.

25 Hollman, A. L., Tchounwou, P. B., & Huang, H.-C. (2016). The Association between Gene-Environment Interactions and Diseases Involving the Human GST Superfamily with SNP Variants. International Journal of Environmental Research and Public Health, 13(4). https://doi.org/10.3390/ijerph13040379

26 Ilaghi, M., Kafi, F., Shafiei, M., Zangiabadian, M., & Nasiri, M. J. (2024). Dietary supplementations to mitigate the cardiopulmonary effects of air pollution toxicity: A systematic review of clinical trials. PLOS ONE, 19(6), e0304402. https://doi.org/10.1371/journal.pone.0304402

27 India-Aldana, S., Yao, M., Midya, V., Colicino, E., Chatzi, L., Chu, J., Gennings, C., Jones, D. P., Loos, R. J. F., Setiawan, V. W., Smith, M. R., Walker, R. W., Barupal, D., Walker, D. I., & Valvi, D. (2023). PFAS Exposures and the Human Metabolome: A Systematic Review of Epidemiological Studies. Current Pollution Reports, 9(3), 510–568. https://doi.org/10.1007/s40726-023-00269-4

28 Jackson, T. W., Kwee, L. C., Shah, S. H., Hauser, E. R., Kraus, W. E., & Ward-Caviness, C. K. (2025). Accelerated transcriptomic age and susceptibility to traffic-related air pollution among cardiac catheterization patients. Science of The Total Environment, 999, 180293. https://doi.org/10.1016/j.scitotenv.2025.180293

29 Jbaily, A., Zhou, X., Liu, J., Lee, T.-H., Kamareddine, L., Verguet, S., & Dominici, F. (2022). Air pollution exposure disparities across US population and income groups. Nature, 601(7892), 228–233. https://doi.org/10.1038/s41586-021-04190-y

30 Kasdagli, M.-I., Orellano, P., Pérez Velasco, R., & Samoli, E. (2024). Long-Term Exposure to Nitrogen Dioxide and Ozone and Mortality: Update of the WHO Air Quality Guidelines Systematic Review and Meta-Analysis. International Journal of Public Health, 69, 1607676. https://doi.org/10.3389/ijph.2024.1607676

31 Kawamura, T., Higuchi, M., Radak, Z., & Taki, Y. (2025). Exercise as a geroprotector: Focusing on epigenetic aging. Aging (Albany NY), 17(7), 1583–1589. https://doi.org/10.18632/aging.206278

32 Kundu, A., Feore, A., Sanchez, S., Abu-Zarour, N., Sutton, M., Sachdeva, K., Seth, S., Schwartz, R., & Chaiton, M. (2025). Cardiovascular health effects of vaping e-cigarettes: A systematic review and meta-analysis. 111(13). https://doi.org/10.1136/heartjnl-2024-325030

33 Laumbach, R., Meng, Q., & Kipen, H. (2015). What can individuals do to reduce personal health risks from air pollution? Journal of Thoracic Disease, 7(1), 96–107. https://doi.org/10.3978/j.issn.2072-1439.2014.12.21

34 Li, R., Wang, K., Li, M., Liu, H., You, Y., Liu, D., Guo, X., Chen, J., & Wu, S. (2025). Association between ambient air pollution and renal function indicators: A comprehensive systematic review and meta-analysis. Environmental Research, 286, 122841. https://doi.org/10.1016/j.envres.2025.122841

35 Liu, J., Qi, J., Yin, P., Liu, W., He, C., Gao, Y., Zhou, L., Zhu, Y., Kan, H., Chen, R., & Zhou, M. (2024). Rising cause-specific mortality risk and burden of compound heatwaves amid climate change. Nature Climate Change, 14(11), 1201–1209. https://doi.org/10.1038/s41558-024-02137-5

36 Liu, N., Bu, Z., Liu, W., Kan, H., Zhao, Z., Deng, F., Huang, C., Zhao, B., Zeng, X., Sun, Y., Qian, H., Mo, J., Sun, C., Guo, J., Zheng, X., Weschler, L. B., & Zhang, Y. (2022). Health effects of exposure to indoor volatile organic compounds from 1980 to 2017: A systematic review and meta-analysis. Indoor Air, 32(5), e13038. https://doi.org/10.1111/ina.13038

37 Massachusetts Department of Public Health. (2021, July). Clinicians' Experience with Environmental Exposures. Bureau of Environmental Health. https://www.mass.gov/doc/clinicians-experience-with-environmental-exposures-0/download

38 McCabe, M. A., Curnick, J., Kuehn, T., Zorn, A., & Janssen, B. (2025). Understanding Environmental Health Issues to Inform Community Engagement in the Central Midwest. Research Square, rs.3.rs-7410407. https://doi.org/10.21203/rs.3.rs-7410407/v1

39 Miller, G. W. & Banbury Exposomics Consortium. (2025). Integrating exposomics into biomedicine. Science, 388(6745), 356–358. https://doi.org/10.1126/science.adr0544

40 Moore, S. C., Patel, A. V., Matthews, C. E., Gonzalez, A. B. de, Park, Y., Katki, H. A., Linet, M. S., Weiderpass, E., Visvanathan, K., Helzlsouer, K. J., Thun, M., Gapstur, S. M., Hartge, P., & Lee, I.-M. (2012). Leisure Time Physical Activity of Moderate to Vigorous Intensity and Mortality: A Large Pooled Cohort Analysis. PLOS Medicine, 9(11), e1001335. https://doi.org/10.1371/journal.pmed.1001335

41 Murray, C. J. L., Aravkin, A. Y., Zheng, P., Abbafati, C., Abbas, K. M., Abbasi-Kangevari, M., Abd-Allah, F., Abdelalim, A., Abdollahi, M., Abdollahpour, I., Abegaz, K. H., Abolhassani, H., Aboyans, V., Abreu, L. G., Abrigo, M. R. M., Abualhasan, A., Abu-Raddad, L. J., Abushouk, A. I., Adabi, M., … Lim, S. S. (2020). Global burden of 87 risk factors in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. The Lancet, 396(10258), 1223–1249. https://doi.org/10.1016/S0140-6736(20)30752-2

42 National Academies of Sciences, E., Division, H. and M., Studies, D. on E. and L., Practice, B. on P. H. and P. H., Toxicology, B. on E. S. and, & Outcomes, C. on the G. on P. T. and H. (2022). Potential Health Effects of PFAS. In Guidance on PFAS Exposure, Testing, and Clinical Follow-Up (pp. 3, Potential Health Effects of PFAS). National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK584690/

43 Oblak, L., van der Zaag, J., Higgins-Chen, A. T., Levine, M. E., & Boks, M. P. (2021). A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing Research Reviews, 69, 101348. https://doi.org/10.1016/j.arr.2021.101348

44 Pande, A., Kinkade, C. W., Prout, N., Chowdhury, S. F., Rivera-Núñez, Z., & Barrett, E. S. (2024). Prenatal exposure to synthetic chemicals in relation to HPA axis activity: A systematic review of the epidemiological literature. Science of The Total Environment, 956, 177300. https://doi.org/10.1016/j.scitotenv.2024.177300

45 Panni, T., Mehta, A. J., Schwartz, J. D., Baccarelli, A. A., Just, A. C., Wolf, K., Wahl, S., Cyrys, J., Kunze, S., Strauch, K., Waldenberger, M., & Peters, A. (2016). Genome-Wide Analysis of DNA Methylation and Fine Particulate Matter Air Pollution in Three Study

Populations: KORA F3, KORA F4, and the Normative Aging Study. Environmental Health Perspectives, 124(7), 983–990. https://doi.org/10.1289/ehp.1509966

46 Pant, R., Mathpal, N., Chauhan, R., Singh, A., & Gupta, A. (2024). A Review of Mercury Contamination in Water and Its Impact on Public Health. In N. Kumar (Ed.), Mercury Toxicity Mitigation: Sustainable Nexus Approach (pp. 93–115). Springer Nature Switzerland. https://doi.org/10.1007/978-3-031-48817-7_4

47 Pasupathi, P., Bakthavathsalam, G., Rao, Y. Y., & Farook, J. (2009). Cigarette smoking—Effect of metabolic health risk: A review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 3(2), 120–127. https://doi.org/10.1016/j.dsx.2009.02.006

48 Peled, R. (2011). Air pollution exposure: Who is at high risk? Atmospheric Environment, 45(10), 1781–1785. https://doi.org/10.1016/j.atmosenv.2011.01.001

49 Peters, A., Nawrot, T. S., & Baccarelli, A. A. (2021). Hallmarks of environmental insults. Cell, 184(6), 1455–1468. https://doi.org/10.1016/j.cell.2021.01.043

50 Prata, J. C., da Costa, J. P., Lopes, I., Duarte, A. C., & Rocha-Santos, T. (2020). Environmental exposure to microplastics: An overview on possible human health effects. Science of The Total Environment, 702, 134455. https://doi.org/10.1016/j.scitotenv.2019.134455

51 Quach, A., Levine, M. E., Tanaka, T., Lu, A. T., Chen, B. H., Ferrucci, L., Ritz, B., Bandinelli, S., Neuhouser, M. L., Beasley, J. M., Snetselaar, L., Wallace, R. B., Tsao, P. S., Absher, D., Assimes, T. L., Stewart, J. D., Li, Y., Hou, L., Baccarelli, A. A., … Horvath, S. (2017). Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging (Albany NY), 9(2), 419–437. https://doi.org/10.18632/aging.101168

52 Rana, S. V. S. (2014). Perspectives in Endocrine Toxicity of Heavy Metals—A Review. Biological Trace Element Research, 160(1), 1–14. https://doi.org/10.1007/s12011-014-0023-7

53 Rappaport, N., Schweickart, A., Hood, L., & Price, N. D. (2026). We wait for disease to shout—What if we listened when biology whispered? Cell Systems, 17(2). https://doi.org/10.1016/j.cels.2025.101509

54 Reynolds, C. M. E., Mack, J. B., O'Connor, L., & McAvoy, H. (2024). The effects of vaping on children and adolescent health: A review of systematic reviews. The Lancet, 404, S87. https://doi.org/10.1016/S0140-6736(24)02008-7

55 Riggs, D. W., Malovichko, M. V., Gao, H., McGraw, K. E., Taylor, B. S., Krivokhizhina, T., Rai, S. N., Keith, R. J., Bhatnagar, A., & Srivastava, S. (2022). Environmental exposure to volatile organic compounds is associated with endothelial injury. Toxicology and Applied Pharmacology, 437, 115877. https://doi.org/10.1016/j.taap.2022.115877

56 Ryoo, S.-W., Choi, B.-Y., Son, S.-Y., Lee, J.-H., Min, J.-Y., & Min, K.-B. (2025). Lead and cadmium exposure was associated with faster epigenetic aging in a representative sample of adults aged 50 and older in the United States. Chemosphere, 374, 144194. https://doi.org/10.1016/j.chemosphere.2025.144194

57 Sears, C. G., Liu, Y., Lanphear, B. P., Buckley, J. P., Meyer, J., Xu, Y., Chen, A., Yolton, K., & Braun, J. M. (2024). Evaluating Mixtures of Urinary Phthalate Metabolites and Serum Per-/Polyfluoroalkyl Substances in Relation to Adolescent Hair Cortisol: The HOME Study. American Journal of Epidemiology, 193(3), 454–468. https://doi.org/10.1093/aje/kwad198

58 Simonds, N. I., Ghazarian, A. A., Pimentel, C. B., Schully, S. D., Ellison, G. L., Gillanders, E. M., & Mechanic, L. E. (2016). Review of the Gene-Environment Interaction Literature in Cancer: What Do We Know? Genetic Epidemiology, 40(5), 356–365. https://doi.org/10.1002/gepi.21967

59 Singer, M. (2011). Down Cancer Alley: The Lived Experience of Health and Environmental Suffering in Louisiana's Chemical Corridor. Medical Anthropology Quarterly, 25(2), 141–163. https://doi.org/10.1111/j.1548-1387.2011.01154.x

60 Tee Lewis, P. G., Chiu, W. A., Nasser, E., Proville, J., Barone, A., Danforth, C., Kim, B., Prozzi, J., & Craft, E. (2023). Characterizing vulnerabilities to climate change across the United States. Environment International, 172, 107772. https://doi.org/10.1016/j.envint.2023.107772

61 Thangaraj, S. V., Ogwara, C., & Padmanabhan, V. (2026). Role of antioxidant vitamins in mitigating the health risks from environmental toxicant exposures: A narrative review. Journal of the Endocrine Society, 10(3), bvag017. https://doi.org/10.1210/jendso/bvag017

62 Thomson, E. M. (2019). Air Pollution, Stress, and Allostatic Load: Linking Systemic and Central Nervous System Impacts. Journal of Alzheimer's Disease, 69(3), 597–614. https://doi.org/10.3233/JAD-190015

63 Tsai, W.-L., Mcinroe, E. M., Jalowska, A. M., Keeler, C. Y., Cleland, S. E., O'Lenick, C. R., Spero, T. L., Schneider, A., & Rappold, A. G. (2026). Characterizing adaptive capacity for the future heat-related cardiovascular morbidity burden in U.S. Metropolitan areas. Environment International, 207, 110022. https://doi.org/10.1016/j.envint.2025.110022

64 U.S. Environmental Protection Agency. (2016). U.S. EPA. Integrated Science Assessment (ISA) for Oxides of Nitrogen – Health Criteria (Final Report). EPA/600/R-15/068, 2016.

65 U.S. Environmental Protection Agency. (2019). U.S. EPA. Integrated Science Assessment (ISA) for Particulate Matter (Final Report, Dec 2019). EPA/600/R-19/188, 2019.

66 U.S. Environmental Protection Agency. (2020). U.S. EPA. Integrated Science Assessment (ISA) for Ozone and Related Photochemical Oxidants (Final Report, Apr 2020). EPA/600/R-20/012, 2020.

67 Veenendaal, M., Painter, R., de Rooij, S., Bossuyt, P., van der Post, J., Gluckman, P., Hanson, M., & Roseboom, T. (2013). Transgenerational effects of prenatal exposure to the 1944–45 Dutch famine. BJOG: An International Journal of Obstetrics & Gynaecology, 120(5), 548–554. https://doi.org/10.1111/1471-0528.12136

68 Vethaak, A. D., & Legler, J. (2021). Microplastics and human health. Science, 371(6530), 672–674. https://doi.org/10.1126/science.abe5041

69 Walker, D. I., Valvi, D., Rothman, N., Lan, Q., Miller, G. W., & Jones, D. P. (2019). The Metabolome: A Key Measure for Exposome Research in Epidemiology. Current Epidemiology Reports, 6(2), 93–103. https://doi.org/10.1007/s40471-019-00187-4

70 Ward-Caviness, C. K. (2019). A review of gene-by-air pollution interactions for cardiovascular disease, risk factors, and biomarkers. Human Genetics, 138(6), 547–561. https://doi.org/10.1007/s00439-019-02004-w

71 Ward-Caviness, C. K., Nwanaji-Enwerem, J. C., Wolf, K., Wahl, S., Colicino, E., Trevisi, L., Kloog, I., Just, A. C., Vokonas, P., Cyrys, J., Gieger, C., Schwartz, J., Baccarelli, A. A., Schneider, A., & Peters, A. (2016). Long-term exposure to air pollution is associated with biological aging. Oncotarget, 7(46), 74510–74525. https://doi.org/10.18632/oncotarget.12903

72 Ward-Caviness, C. K., Russell, A. G., Weaver, A. M., Slawsky, E., Dhingra, R., Kwee, L. C., Jiang, R., Neas, L. M., Diaz-Sanchez, D., Devlin, R. B., Cascio, W. E., Olden, K., Hauser, E. R., Shah, S. H., & Kraus, W. E. (2020). Accelerated epigenetic age as a biomarker of cardiovascular sensitivity to traffic-related air pollution. Aging, 12(23), 24141–24155. https://doi.org/10.18632/aging.202341

73 Weston, W. C., Bind, M. A., Cascio, W. E., Devlin, R. B., Diaz-Sanchez, D., & Ward-Caviness, C. K. (2024). Accelerated aging and altered subclinical response to ozone exposure in young, healthy adults. Environmental Epigenetics, 10(1), dvae007. https://doi.org/10.1093/eep/dvae007

74 Wild, C. P. (2005). Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology. Cancer Epidemiology, Biomarkers & Prevention, 14(8), 1847–1850. https://doi.org/10.1158/1055-9965.EPI-05-0456

75 World Health Organization. Regional Office for Europe. (2021). Review of evidence on health aspects of air pollution: REVIHAAP project: Technical report. https://iris.who.int/items/169a6d1f-3478-4675-a73d-439e71214908

76 Xu, J., Wang, Q., Anikeeva, O., Zhu, P., Bi, P., & Huang, C. (2025). Effects of extreme heat on physiology, morbidity, and mortality under climate change: Mechanisms and clinical implications. https://doi.org/10.1136/bmj-2025-084675

77 Yilmaz, B., Terekeci, H., Sandal, S., & Kelestimur, F. (2020). Endocrine disrupting chemicals: Exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. Reviews in Endocrine and Metabolic Disorders, 21(1), 127–147. https://doi.org/10.1007/s11154-019-09521-z

78 Zhang, P., Carlsten, C., Chaleckis, R., Hanhineva, K., Huang, M., Isobe, T., Koistinen, V. M., Meister, I., Papazian, S., Sdougkou, K., Xie, H., Martin, J. W., Rappaport, S. M., Tsugawa, H., Walker, D. I., Woodruff, T. J., Wright, R. O., & Wheelock, C. E. (2021). Defining the Scope of Exposome Studies and Research Needs from a Multidisciplinary Perspective. Environmental Science & Technology Letters, 8(10), 839–852. https://doi.org/10.1021/acs.estlett.1c00648

79 Zhang, Z., Sheng, N., Qu, Y., Xue, Z., Zhao, F., Wu, B., Lv, C., Dong, F., Wang, J., Song, H., Sun, Q., Zhang, M., Long, F., Li, Y., Ji, S., Li, Z., Zhang, X., Fu, H., Li, K., … Shi, X. (2025). Dietary Diversity Modified the Association of Per- and Polyfluoroalkyl Substances with Accelerated Biological Aging: Evidence from the China National Human Biomonitoring Study. Environmental Science & Technology, 59(16), 7877–7889. https://doi.org/10.1021/acs.est.4c13048

ABOUT THIS RESEARCH

This Keynote Perspective was developed by Healthspan Horizons, an initiative based at the Buck Institute for Research on Aging. The work reflects a unified research and systems design effort to make healthspan measurable, computable, and actionable.

Healthspan Horizons advances a federated, AI-enabled framework for integrating multi-omic, clinical, behavioral, and environmental data to support long-term resilience and healthy aging.

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