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RESEARCH ARTICLE

# A glossary for social-to-biological research

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Research has shown that our socially structured experiences elicit a biological response, leading to the observation that numerous biomarkers (objective biological measures that are representative of various biological processes) are socially patterned. This 'social-to-biological' research is of interest to researchers across multiple disciplines and topics and especially to those with an interest in understanding the biological embodiment of the 'social environment'.

Combining social and biomarker data is also of relevance to those examining the biological determinants of social behaviours (for example, the relationship between genetics and certain behaviours like smoking). However, as much of the research involving biomarkers and social data are multidisciplinary, researchers need to understand why and how to optimally use and combine such data. This article provides a resource for researchers by introducing a range of commonly available biomarkers across studies and countries. Because of the breadth of possible analyses, we do not aim to provide an exhaustive and detailed review of each. Instead, we have structured the glossary to include: an easy-to-understand definition; a description of how it is measured; key considerations when using; and an example of its use in a relevant social-to-biological study. We have limited this glossary to biomarkers that are available in large health and social surveys or population-based cohort studies and focused on biomarkers in adults. We have structured the glossary around the main physiological systems studied in research on social to biological transition and those that go across systems and highlight some basic terms and key theoretical concepts.

**Keywords** biomarkers • embodiment • physiology • social to biological

**Key messages**

- Increasingly, researchers are interested in combining social and biological data in their studies.
- Researchers need to understand why and how to best make use of combining such data.
- This article provides a novel biomarker glossary to aid implementation in studies.
- We present theoretical and practical information on collecting and analysing biomarkers from multiple physiological systems.

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## Introduction

*A glossary for social-to-biological research*

With any emerging and/or interdisciplinary field like social-to-biological research, there can be gaps in the knowledge base around why and how to best make use of combining data from different disciplines. Barriers to successfully integrating social and biomarker data include unfamiliar biological terminology, a lack of experience and confidence in handling (sometimes large) complex and unfamiliar data, and a lack of knowledge and experience in interpreting biological data in a nuanced manner that correctly considers the appropriate limitations. Here we have provided an introductory glossary to assist researchers by providing them with definitions and theory, introductory information about biomarkers, appropriate further reading, and the mechanisms relevant to studies that link social and biological data. This article is intended as a resource for those starting social-to-biological research through to those who are well established in the field. Each biomarker or concept discussed here

merits its own individual review investigating the links with social and economic factors such as socioeconomic position. However, our aim is not to provide an exhaustive and detailed review of each, but to provide a structured glossary that includes: an easy-to-understand definition; a description of the measurement or technology; key considerations when using; and an example of use in a relevant social-to-biological study.

As there are thousands of potential biomarkers that could be included, we have limited this glossary to biomarkers that are more readily available in large health and social surveys/cohorts of the adult general population. While many of the biomarkers and concepts may be relevant to children and adolescents, the data and research on biomarkers in younger people is much more limited than in adults (Savage and Everett, 2010) and we have therefore focused on measures and evidence in adults. We have structured the glossary around the main human physiological systems studied in research on social to biological transition. We also highlight some basic terms and key theoretical concepts, some of which are also measures themselves, for example, allostatic load.

### *Biosocial or social-to-biological?*

Biosocial research can be considered a 'broad concept referencing the dynamic, bidirectional interactions between biological phenomena and social relationships and contexts, which constitute processes of human development over the life course' (Harris and McDade, 2018). Biosocial research is an emerging multidisciplinary field, with researchers from across the social, life and health sciences. The field can be split into two main interests, based on the hypothesised direction of effect. First, there are investigators who focus on understanding the biological embodiment of the 'social environment' (Blane et al, 2013) (see Embodiment section). This area of research is sometimes termed 'social-to-biological' (Blane et al, 2013). Social-to-biological research places much emphasis on the interaction between biological and social experiences throughout life, and the influence of this interaction on the individual's health outcome. It is a holistic approach to disease aetiology, studying the long-term effects of physical and social exposures on health and wellbeing, and therefore, it draws no firm boundary between what is biological or physical, and what is social or cultural. Second, there are investigators who focus on how biology impacts people's social circumstances, for example, how genetics influence educational attainment, often referred to as 'biosocial' or 'sociobiological' research (Meloni et al, 2016). While this article can be read and hopefully appreciated by researchers in both areas, we focus here on social-to-biological research given our expertise and interest in this area and the core audience of this journal.

### *The importance of this field of inquiry*

The relative success of humans as a species is linked to our adaptability, which may be afforded by our complex social structures interacting with complex biological systems. With the advent of large population datasets containing data on social conditions as well as chemical, physical and biological measures, we can investigate the relationships between factors that are external and internal to the body. This growing field of multidisciplinary research has shown that our socially structured experiences elicit

a biological response, leading to the observation that numerous biological measures are socially patterned. This converges with research from biological anthropology, suggesting that human biology is at least partly socially constructed (Lock, 1993). Here, these 'local biologies' refer to how social and biological processes are 'permanently entangled throughout life, ensuring a degree of biological difference among humans everywhere that typically has little or no significance but at times bears profoundly on wellbeing' (Lock, 2017).

The first reason for this type of research is to understand the social influences on human biology. It is well established that health is socially patterned, and researchers are interested in understanding how the wider social and ecological context gets transduced at a more fundamental physiological level – from society to cells. A second reason may be more closely linked to understanding the construction of health over the life course and across human environments. Biological measures allow us to unveil the workings of our internal milieu before the manifestation of disease or sickness. The usual or normal functioning of our biological systems can now be more easily examined, allowing us to observe similarities and differences across social contexts and over time (Benzeval et al, 2016). Access to these data open up new opportunities for defining and assessing what health is or is not, and what we define as sickness or disease. A third reason for this field of enquiry is that it may help us to better understand the construction of social inequalities in health. Socioeconomic differences in health outcomes are ubiquitous across contexts, over time, and remain stubbornly persistent despite public health efforts to reduce them. Combining biological outcomes with social data allows the social environment to be repositioned as a central factor in the modification of biological functioning, making it a target for intervention, in contrast to pharmacological/therapeutic approaches centred on a single biomarker. Examining social-to-biological processes from early life, and even intergenerationally, may help us to understand how our societies and social conditions could be altered for the betterment of our health, and to reduce health inequalities. Fourth and finally, molecular and cellular-level biological processes that do not substantially impair functioning are less likely to influence socioeconomic circumstances (reverse causation) (Kubzansky et al, 2014).

### *Important considerations before reading further*

Where relevant, we mention 'normal' values or ranges for some biomarkers. These values are typically based on clinical norms about (pre-)disease states, but there is an intrinsic bias in these 'norms' based on a 'Western' bias, with many of the studies used to validate these 'norms' coming from largely white, US/European studies over the last 50 years. We have attempted to provide examples of use from other contexts where possible. As we cannot capture all aspects of this emerging field, we have chosen to focus on some of the common/key biomarkers and concepts relevant to linking with social markers. Readers are encouraged to review the websites, study profiles and/or working papers/technical reports for their studies of interest. For example, the UK Household Longitudinal Study (UKHLS, also known as Understanding Society) provides a detailed section of its website for the biomarker and health data (Understanding Society, 2024), which includes a detailed User Guide (Institute for Social and Economic Research, 2022). There is also a study profile that highlights the biomarkers included and their potential value (Buck and McFall, 2012). Similarly, the

Centre for Longitudinal Studies provides information on the biomedical sweeps of the UK national cohort studies (Centre for Longitudinal Studies, 2022) and a guide is also available for biomarker data in many UK studies (Ruiz et al, 2017). Finally, the US-led Biomarker Network highlights biomarkers measured across some of the world's leading ageing studies (The Biomarker Network, 2021).

We only include descriptions of biomarkers in adults, although in many cases early exposures will be important, however datasets with biological measures during childhood and adolescence are rare. In addition, there are limited studies that have measured biomarker data longitudinally, except for measures like blood pressure and body mass that are the least invasive, relatively cheap and widely used in clinical practice. This is a clear gap in our knowledge in understanding how the social and biological interact (Harris and Schorpp, 2018). Finally, we do not discuss the various datasets where it is possible to find social and biomarker measures, although we have included examples of use for each biomarker that readers can explore and highlighted some key dataset resources.

Next, we highlight biological concepts and terms relevant to social science and social epidemiology. This is followed by some descriptions of how biomarker samples are typically collected, before we present the glossary. The glossary is structured first exploring markers that fit within single physiological systems, although many interact with and influence markers from other systems. We then move onto cross-system measures, travelling downstream from omics to cross-system wear-and-tear (allostatic load and biological ageing) and finally 'external' measures of body shape and size.

## Relevant biological concepts

*Embodiment*

First introduced in social epidemiology by Nancy Krieger, embodiment refers to how humans 'literally incorporate, biologically, the world in which we live, including our societal and ecological circumstances', insisting on the nature of human bodies as active and engaged entities (Krieger, 2005). Embodiment occurs via two broad types of socially distributed mechanisms: first, mechanisms of 'exogenous' origin through which entities or conditions external to the body either enter the body and elicit a physiological response from it (inert or living entities like foodstuffs, asbestos, viruses, bacteria, pollutants, and so on) or lead to physical harm (injuries, accidents) or exertion (movements, actions). This concerns environmental exposures such as pollution, pesticides, work exposures and behaviours such as tobacco, alcohol and diet. And, second, mechanisms of 'endogenous' origin through which sensory interpretations of interactions with the environment elicit responses from 'internal' molecules from the body mainly linked to stress perception and stress response systems, as well as cognitive and psychological functions. In terms of exposures this concerns especially psychosocial exposures, such as adversities during childhood (trauma, sexual abuse, physical violence, neglect), occupational constraints, social support, social isolation and experiencing discrimination, whether related to age, gender, social class, skin colour, sexual orientation or disability. The two types of exposures may also interact and affect each other along the life course (Kelly-Irving and Delpierre, 2017; 2021). Due to its dynamic nature, embodiment can vary over time. It is therefore inextricably linked

to the life course, and thus to the life course approach in epidemiology (detailed in the following section) (Kelly-Irving and Delpierre, 2021).

### *Life course models*

The life course approach provides a relevant conceptual and methodological framework for social-to-biological research as it typically refers to processes and mechanisms occurring over the human life span that vary in relation to human development and socially (and biologically) defined life stages and transitions. In the context of epidemiology, the life course framework is based on several fundamental concepts. First, individuals accumulate risk throughout their lives, from the foetal environment onwards, rendering them (more or less) susceptible to adult chronic disease. Second, individuals may experience critical periods at specific points in the life course where an exposure has particularly significant and lasting effects on the person's biological or social life (Kuh and Ben-Shlomo, 1997; Ben-Shlomo and Kuh, 2002). Finally, individuals can move up or down the social gradient throughout their lifetime, and this social mobility can have beneficial or detrimental effects on their health (Hallqvist et al, 2004). The life course perspective in epidemiology is grounded in the underlying biological concepts from the foetal origin hypothesis, that conditions like obesity, hypertension, hyperlipidaemia and Type 2 diabetes were associated with malnutrition or some other cause of growth restriction during early development, if there was later exposure to a contrasting high-energy diet (Barker et al, 2002).

## Main sources of biomarkers

A biological marker, or biomarker, can be defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' (Biomarkers Definitions Working Group, 2001). Most biomarkers available in health and social surveys come from the extraction of blood, but can also be measured in urine, saliva and hair samples, as well as through anthropometric assessments, for example, muscle strength.

### *Venous blood*

Venepuncture is the technique whereby a sample of blood is taken from a vein using a hypodermic needle and collected in a specific tube depending on the biomarkers to be tested (Kringelbach et al, 2018). Plasma is the fluid that suspends blood cells and forms part of the whole blood sample. The most common collection method for plasma is to collect blood in a tube containing an anti-coagulant additive, the most common being EDTA, to preserve the sample and prevent coagulation. The tube is then spun in a centrifuge to create three distinctive layers (referred to as blood fractionation): the plasma, the buffy coat (white blood cells and platelets) and the red blood cells (erythrocytes). If the blood is not collected in a tube with a relevant anti-coagulant, it is difficult to complete blood fractionation that produces clearly separated layers. For some biomarkers, it may not be necessary to separate the plasma, and instead a serum sample is sufficient or required. Serum is the fluid and its component parts of blood which do not play a role in clotting. Blood is withdrawn in the same

way as described previously but collected in a tube without any additives like EDTA ('serum tube') as this allows clotting to take place. The sample is then centrifuged. The spun tube will contain serum and clotted blood which can be separated for testing. While most of the components of plasma and serum are the same, plasma contains the clotting factor fibrinogen (see Fibrinogen section) which serum does not (due to blood clotting).

*Capillary samples*

Blood (in smaller volumes) can also be collected by a small prick of the skin, known as a capillary sample. These pricks can be taken from the finger (typically adults) or heel (typically children). In studies employing this method is it now increasingly common to blot this blood onto a specially designed card. These samples are known as dried blood spots (DBS) and are a good choice for studies with the challenges of large sample size and longitudinal assessment, including in hard-to-reach populations (McDade et al, 2007; Brindle et al, 2014). However, DBS and venous blood samples do not always show consistent results. DBS can contain low amounts of the analytes of interest due to the small volume collected and not all biomarkers have yet been tested and validated using DBS (Brindle et al, 2014).

*Urine, saliva and hair*

Non-invasive sampling techniques are also possible and may offer one mechanism to limit non-response/lack of consent when respondents do not want (or are unable) to provide a blood sample. However, there are limits on validated tests available for some biomarkers and they can give measurements over different timescales compared to blood (both a positive and potentially a negative for comparisons/interpretation) (El-Farhan et al, 2017). For example, cortisol (see Cortisol section) can be measured in blood, urine, saliva and hair. Blood samples and saliva give a measure at the point of sampling, urine over the previous 24 hours and hair over previous months (up to six months) (Adam and Kumari, 2009; Russell et al, 2012; El-Farhan et al, 2017).

## Key physiological systems

The human body consists of 11 physiological systems: the circulatory (cardiovascular), digestive, endocrine, immune, integumentary, muscular, nervous, renal (excretory), reproductive, respiratory and skeletal systems. There are biomarkers available across all these systems, but (as noted in the opening paragraph) we focus on those we deem the most relevant to potential social-to-biological research that are readily available in large health and social surveys/cohorts of the adult general population and some of the main physiological systems theorised and studied in research on social to biological transitions (Kubzansky et al, 2014; Harris and Schorpp, 2018; McDowell, 2023). These include circulatory (cardiovascular), digestive, endocrine, immune, muscular and respiratory systems. This is not to exclude the value already obtained, or obtainable in future studies, from exploring a wider range of markers and systems, but rather to initiate thought and discussion, grounded with strong evidence, on what possibilities are open to social researchers wanting to explore the biological consequences of our social environments.

## Circulatory (cardiovascular) system markers

The purpose of the circulatory system is to deliver oxygenated blood to the cells and organ systems in the body, as well as to transport nutrients, hormones and waste products. In carrying out these functions, the circulatory system interacts continually with the digestive, nervous, renal and respiratory systems. The circulatory system consists of the heart, arteries, veins and capillaries. Markers include blood pressure, pulse pressure, heart rate and homocysteine.

### *Diastolic and systolic blood pressure*

Diastolic blood pressure (dBP) is the pressure in the blood vessels when the heart rests between beats, while systolic blood pressure (sBP) is the pressure in the blood vessels when the heart beats. 'Blood pressure' as a health measure is reported as the sBP 'over' dBP (for example, 120 over 80). Both numbers are measured using either a manual or a digital blood pressure monitor (sphygmomanometer) and measured in millimetres of mercury (mmHg). Two or three readings on one arm, with the participant seated and with a short gap between measures, are typically recorded and the mean value used. Often, hypertensive medication use (used to lower blood pressure) is also recorded and factored into analyses/interpretations. Both high and low blood pressure readings are linked with negative health outcomes, although typically researchers will be most interested in elevated levels that signify hypertension and risk for cardiovascular diseases, especially raised sBP (Rapsomaniki et al, 2014). Clinical cut-offs are often used to distinguish between 'normal' and 'high' blood pressure, which for hypertension is 130/80mmHg and above in the US following a change in the definition (from 140/90mmHg which remains the standard in the UK, for example) (National Institute for Health and Care Excellence, 2019). However, 'ideal' or 'normal' blood pressure is considered less than 120/80mmHg by the American Heart Association (American Heart Association, 2017). Example of use: (Diez Roux et al, 2002).

### *Pulse pressure*

Pulse pressure is the difference between sBP and dBP, which represents the force that the heart generates each time it contracts. It is calculated by subtracting dBP from sBP and is measured in mmHg. Pulse pressure has been shown to be a risk marker of heart disease, most likely due to its function as a marker of arterial stiffness and arterial fibrillation (Franklin et al, 1999; Mitchell et al, 2007; Franklin and Wong, 2013). Example of use: (Schooling et al, 2007).

### *Heart rate*

Heart rate is a measure of electrically stimulated contractions of the heart equal to heartbeats per minute (bpm), with a normal resting range of 60–100 bpm (British Heart Foundation, 2020). Measurement is a count in bpm and can be estimated manually via the pulse in the wrist or it may be measured using a heart rate monitor. Elevated resting heart rate has been shown to be a risk factor for mortality independent of age, physical fitness, leisure-time physical activity and other cardiovascular risk

factors (smoking, alcohol, body mass index [BMI], blood pressure and cholesterol) (Jensen et al, 2013). Example of use: (Hickson et al, 2012).

*Homocysteine*

Raised homocysteine (tHcy) has been recognised as a risk factor for atherosclerosis (plaques in blood vessels) (Lentz, 2001), cardiovascular diseases (Whincup et al, 1999; Wald et al, 2002), and cognitive decline, dementia and Alzheimer's disease (Smith et al, 2018). tHcy can be measured in plasma (and serum, but plasma measurement is more common) using specific tHcy assays and is typically recorded as μmol/L. Unlike the cardiovascular markers already described, which are basic measures of cardiovascular function (cardiac output or arterial pressure), tHcy is derived from a blood test that measures amino acids. In analysis, folate levels/supplementation are adjusted for (if collected and especially important in pregnant women) as low levels of folic acid/folate increases homocysteine. Normal levels are deemed to be below 15 μmol/L in plasma. Example of use: (Muennig et al, 2007).

## Digestive system markers

The digestive system is designed to convert food into its constituent macro- and micro-nutrient parts so that they can be absorbed into the bloodstream and used by the rest of the body. As well as the stomach, intestines and mouth being part of the system, the pancreas, liver and gallbladder are also key components. In carrying out its function the digestive system interacts with the circulatory, endocrine, excretory and nervous systems. Biomarkers include those that can be classed as 'metabolic' and/or 'dietary', such as adiponectin, fasting glucose, glycated haemoglobin, cholesterol (HDL, LDL and Total), leptin and triglycerides, as well as the gut microbiome.

*Adiponectin*

Adiponectin is an adipose-specific (body fat) plasma protein that is secreted by fat cells known as adipocytes, essentially the main energy storage site in the human body. Adiponectin is involved in regulating glucose levels, lipid metabolism and insulin sensitivity (Nguyen, 2020). Low adiponectin levels can indicate metabolic syndrome (Ryo et al, 2004). Multiple assays can measure adiponectin, with normal range between 0.5 and 30μg/ml. Levels below 4μg/ml are associated with metabolic syndrome (Ryo et al, 2004). Example of use: (Davis et al, 2016).

*Fasting glucose*

Glucose is a type of sugar that provides energy to cells in our bodies. We get glucose from our diets, largely from the intake of carbohydrates. Following the breakdown of food into glucose, this signals the production of insulin by the pancreas, as insulin facilitates glucose entering cells by binding to specific receptors on the cell surface. Diabetes occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces (WHO, 2023). Glucose is often measured in fasted samples so that recent food/drink intake does not interfere with the measurement achieved and is used to assess diabetes risk or for monitoring

diabetics' control of their blood sugar. Typically glucose has been measured via a blood sample using an assay (Ruiz et al, 2017), but it can also be measured 'live' using a glucose meter that requires a pin-prick blood sample to be collected on the test strip and measured using the meter (Pickering and Marsden, 2014). More recently we have also seen the increased use of continuous glucose monitoring (CGM) systems, where a tiny sensor is inserted under the skin and transmits data to a receiver worn by the subject (or straight to a smartphone app) (Tang et al, 2016). Normal fasting glucose levels are between 4 and 5.9mmol/l while fasting levels above 7mmol/l indicate diabetes. Levels between 5.9 and 6.9mmol/L indicate prediabetes. Low levels can also be a marker of risk for low blood sugar levels in diabetic patients. Example of use: (Nakanishi, 2001).

### *Glycated haemoglobin (HbA1c)*

Glycated haemoglobin, also known as HbA1c, is a common biomarker of diabetes and prediabetes, similar to fasting glucose. Unlike fasting glucose HbA1c represents a measure of blood glucose level over the previous 2–3 months and is measured as the percent of haemoglobin (protein in red blood cells) that is glycated (has sugar attached) using a technique called HPLC (High-Performance Liquid Chromatography) that is standard in most laboratories/hospitals (Nathan et al, 2008). Percentage HbA1c can also be measured as mmol/mol, although this is less common. Values of 6.5% and above indicate diabetes, with 6–6.4% indicating prediabetes (WHO, 2011). Example of use: (Mutyambizi et al, 2019).

### *Cholesterol (HDL, LDL and total)*

Cholesterol is found in body tissues and blood plasma of vertebrates and is an essential structural component of animal cell membranes (Schade et al, 2020). Cholesterol is mostly produced by hepatic (liver) cells but can also come from the diet of animal origins and serves as a precursor for the steroid hormones (testosterone and oestrogen) and vitamin D. Cholesterol is carried in the blood in particles named lipoproteins, a complex of lipid and protein. The lipoproteins are classified according to their density and the most common are lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Total cholesterol is the combined amount of LDL and HDL cholesterol in blood. Abnormal levels of cholesterol have been observed in various diseases including cardiovascular diseases, Type 2 diabetes, liver diseases and others. Epidemiological studies have shown that elevated levels of LDL cholesterol are associated with an increased risk of developing blockages in the coronary arteries, whereas elevated levels of HDL cholesterol reduce that risk (Jung et al, 2022). Accumulation of cholesterol on artery walls is known as atherosclerosis, with the resulting plaques reducing blood flow through the arteries, increasing risks of heart attacks and stroke.

A variety of factors can affect cholesterol levels including diet, weight, physical activity, age and gender, medical conditions and treatment (Muga et al, 2019). For instance, it has been shown that positive health behaviours such as physical activity (Mendoza et al, 2022) and diet (Huang et al, 2011) act as protective factors against hyperlipidaemia, while cigarette smoking (Chelland Campbell et al, 2008) is known to have a negative effect on blood lipids. Various methods for serum cholesterol

concentration, including ultracentrifugation, electrophoresis, high performance lipoprotein chromatography, precipitation-based method, direct measuring method and nuclear magnetic resonance, are available (Hafiane and Genest, 2015; Li et al, 2019). Normal values of total cholesterol should be 5mmol/L or lower in healthy adults, while LDL levels should be 3mmol/L or lower and HDL-cholesterol levels above 1.0 and 1.2mmol/L in men and women, respectively (De Backer et al, 2003). Example of use: (Strand and Tverdal, 2006).

*Leptin*

Leptin is a hormone produced mainly by fat (adipose) cells in the body, and levels have been shown to be positively correlated with body fat and therefore long-term energy stores (Considine et al, 1996). More acutely, leptin levels can also fluctuate depending on calorie intake, especially fasting or starvation (Considine et al, 1996). The most significant roles of leptin include regulation of energy homeostasis (acting on the brain to regulate appetite and influence food intake), neuroendocrine function (fasting induces rapid decline in leptin, triggering the neuroendocrine response to acute energy deprivation) and metabolism (in cases of severe leptin deficiency) (Park and Ahima, 2015). The value of measuring leptin remains mixed, with some evidence of links with metabolic syndrome, insulin resistance, fat/body mass and obesity, although the clinical significance of these relationships is questionable at this stage (Grasso, 2022). Much of the research using leptin in social/health surveys and studies has focused on leptin in childhood and adolescence, rather than in adulthood. Leptin can be measured in serum or plasma samples and samples are relatively stable without freezing (approx. 2 months at 4°C), with Radio-ImmunoAssays (RIAs) and ELISAs available to quantify leptin levels (Wallace, 2000). Studies typically adjust for measures of fat or body mass (for example, BMI), sex and time of collection (as leptin peaks late at night and in the morning). Fasting is often not preferable, as concentrations decrease considerably following fasting (as well as massive overfeeding) (Sinha and Caro, 1998). Example of use: (Howe et al, 2010).

*Gut microbiome*

The microbiome has been defined as the collective genome of the microorganisms that live on and inside humans, including on or within the skin, organs, mucous membranes and intestinal tract ('gut') (Hooper and Gordon, 2001; Gilbert et al, 2018). Population-scale data detailing the composition and function of the microbiome has been possible in recent years with rapidly developing technology, allowing us to map the genome of these microbial communities and explore their role in human health and disease (Methé et al, 2012; Proctor et al, 2019; Greenhough et al, 2020). In addition, the broad environmental factors, particularly social conditions, that may influence the microbiome have garnered increasing attention (Herd et al, 2018). There is emerging and increasing evidence that the gut microbiome, the diversity and abundance of microbes in the gastrointestinal tract, is a key element of the microbiome that is causally important for health (for example, changing metabolism) and correlated with gastrointestinal (for example, irritable bowel syndrome) and non-gastrointestinal (for example, obesity) conditions, and even potentially linked with brain development (Radjabzadeh et al, 2017). Imbalances in the composition of bacteria in the gut can occur, causing dysbiosis.

There are three types of dysbiosis, which can often co-occur, consisting of the loss of overall bacterial diversity, the loss of 'good/helpful' bacteria, and the overgrowth of potentially pathogenic bacteria (DeGruttola et al, 2016). Early-life conditions are thought to interact with adult social, economic and health conditions to modify the gut microbiome, resulting in physiological or stress responses that can be harmful under chronic exposure, in turn increasing the risk for morbidity and mortality (Dowd and Renson, 2018; Herd et al, 2018; Amato et al, 2021).

In terms of measurement, the microbiome is assessed by identifying each species of microbe by their genetic profile (typically via their RNA or DNA sequence – see Transcriptomics section). Often faecal samples will be used, but blood samples that measure the so-called 'circulatory microbiome' that can act as a potential proxy for the gut microbiome, although this approach does remain controversial (Whittle et al, 2019). Examples of use: (Bowyer et al, 2019) (faecal samples); (Craven et al, 2021) (blood samples).

### *Triglycerides*

Triglycerides are a combination of three fatty acids and glycerol (a carbohydrate molecule) which we get from our diet and through production in the liver. Triglycerides are important as they fuel our bodies but are also how our bodies store excess calories in fat cells that can be released in between meals to keep energy levels stable. If, however, we consume more calories than we need on a regular basis these triglycerides will continue to be stored and accumulate as body fat (they are the most common type of body fat) (University of Rochester Medical Center, 2020). They can be one sign of metabolic syndrome, which increases the risk of having a heart attack or stroke (Alberti et al, 2009). As triglycerides increase, typically HDL cholesterol levels decrease. Levels can be lowered medically via statins as a side-effect of attempts to lower LDL levels and should be considered when analysing such data. Normal levels are below 150mg/dL with levels above 200mg/dL deemed high and above 500mg/dL very high. Triglycerides can be measured from whole, plasma or serum blood samples (fasting beforehand is not required) using enzyme assays. Example of use: (Shohaimi et al, 2014).

## Endocrine system markers

The endocrine system is a series of glands set up to control growth, development, metabolism and reproduction through the production and secretion of hormones, which are essentially the body's chemical messengers, regulating physiology and behaviour. A range of organs are part of the endocrine system, including the adrenal glands, hypothalamus, pancreas, pituitary gland, ovaries and testes. The endocrine system interacts with all other systems, but especially with the circulatory (transport), nervous (interpreting signals and altering behaviours) and metabolic (regulation of energy metabolism via insulin) systems. Common system markers include cortisol, dehydroepiandrosterone sulfate, dopamine, epinephrine, estradiol and norepinephrine.

### *Cortisol*

Cortisol has many functions including mediating the stress response, but also is involved in the inflammatory response and regulating metabolism. Cortisol secretion

is regulated by the hypothalamic-pituitary-adrenal (HPA) axis. When a stressor is perceived by the brain, the hypothalamus region of the brain releases Corticotrophin Releasing Factor (CRF). CRF is transported to the pituitary gland, situated just below the hypothalamus, which then produces AdrenoCorticoTrophic Hormone (ACTH). ACTH is then transported to the adrenal glands, located on the top of the kidneys. Here, the adrenal glands produce glucocorticoids, including cortisol. In a negative feedback loop, high (enough) levels of cortisol inhibit the release of both ACTH and CRH, thereby reducing circulating cortisol levels over time. The HPA axis follows a circadian rhythm where cortisol levels will be higher in the morning and lower at night (Ramamoorthy and Cidlowski, 2016). The main role cortisol has is to mobilise glucose stored in the liver, aiming to provide a steady supply of energy for the body to deal with the stressor at hand. Cortisol is also involved in numerous other processes following its secretion, such as increasing blood pressure and activating anti-inflammatory pathways and it is these actions that can result in negative health impacts with long-term, chronic exposure to stressors (as opposed to the main function of the stress response in dealing with short-term stressors).

Cortisol can be measured in blood (plasma or serum), urine, saliva or hair (Adam and Kumari, 2009; El-Farhan et al, 2017). Plasma and salivary cortisol samples reflect HPA activity over seconds to minutes prior to collection. Urinary cortisol samples provide can provide samples that range from overnight to 24 hours. Hair cortisol provides a longer window over several months (Pragst and Balikova, 2006). Therefore, the measurement method is key to the research question being asked.

The evidence for links between cortisol and health have shown mixed results, with both low and high serum cortisol levels associated with poor health outcomes/death in patient populations (Reynolds et al, 2010a; 2010b), but no such association in general population studies (Smith et al, 2005; Schoorlemmer et al, 2009; Rod et al, 2010). However, total 24-hour urinary cortisol has been linked with cardiovascular but not non-cardiovascular mortality (Vogelzangs et al, 2010). As well as these patterns with overall cortisol levels, many studies have attempted to focus on diurnal cortisol as a potentially better marker, with higher levels during waking, followed by a decline across the day. A recent systematic review and meta-analysis, for example, found that flatter diurnal cortisol slopes (the degree of change in cortisol from morning to evening over the waking day [Adam and Kumari, 2009]) were associated with poorer health across all 80 studies (Adam et al, 2017). As with sample type, the measure of cortisol itself is an important consideration when formulating and addressing one's research question(s). Example of use: (Cohen et al, 2006b).

### *Dehydroepiandrosterone sulfate*

Dihydroepiandrosterone (DHEA) and its sulfate form (DHEA-S) are the most common steroid hormones in the body, produced by the adrenal gland in response to ACTH release (see Cortisol section for details). Both DHEA and DHEA-S have been identified as markers of stress (Kroboth et al, 1999; Lennartsson et al, 2013; Dutheil et al, 2021), although DHEA-S has attracted more interest due to two key factors making it easier to measure. First, DHEA-S has the benefit of levels not having a circadian rhythm (unlike DHEA) and, second, there is approximately 1,000 times more DHEA-S in the blood compared to DHEA. DHEA-S is commonly measured from serum using an immunoassay although plasma samples can also be used. DHEA-S

levels increase from early childhood until early adulthood, before steadily declining in both men and women (Orentreich et al, 1984). As well as a measure of stress, lower levels of DHEA-S have been found to be associated with increased CVD and all-cause mortality (Barrett-Connor et al, 1986; Sanders et al, 2010). Example of use: (Dowd and Goldman, 2006).

*Catecholamines*

Catecholamines are a type of neurohormone, which are hormones that are produced and released by neuroendocrine cells that receive neuronal (nerve cell) inputs and, consequently, release messenger molecules (hormones) into the blood. Catecholamines are important neurotransmitters in the sympathetic nervous system (SNS), whose primary function is related to the stress response and the body's 'fight or flight response'. Catecholamine release exerts cardiovascular and metabolic effects by stimulating adrenergic receptors (receptors on the surface of cells that are activated when they bind to catecholamines), leading to increased alertness and increasing blood flow into the skeletal muscles to ensure we are ready to move (if needed). Unlike cortisol that is synthesised by the adrenal cortex (outer part of the adrenal gland), catecholamines are synthesised in the adrenal medulla (inner part of the adrenal gland).

Examples of catecholamines include dopamine, epinephrine (also known as adrenaline) and norepinephrine (previously 'noradrenaline'), although epinephrine and norepinephrine are the focus when measuring the stress response. Epinephrine functions predominantly like a hormone, that is, it is released from the adrenal gland into the blood stream, where it is transported to various target tissues. Norepinephrine functions more like a neurotransmitter, primarily produced by the sympathetic nerve fibres, and is released directly to tissue adrenergic receptors (Cryer, 1980). Following a stressor, epinephrine is released and induces a range of physiological changes that include increased heart rate and blood pressure, increased oxygen and glucose and fat release, increasing alertness and supplying energy to the body. As the initial epinephrine release wanes, the HPA axis is activated (see Cortisol section) (Auchus et al, 2011; White and Porterfield, 2013).

Catecholamines can be measured in plasma or urine (urine being less impacted by stress responses at the time of sampling) using a range of techniques, but these typically include specific assays for each marker and/or HPLC chromatography (Peaston and Weinkove, 2004; Guber et al, 2021). There are diurnal patterns in some catecholamines like noradrenaline, stress-induced changes and they can be rapidly altered by smoking, caffeine and certain foods. There is also evidence of posture effects on plasma concentrations (Saar and Gordon, 1979). Participants are usually asked to fast for approximately 12 hours prior to sample collection and or asked to collect 24-hour or overnight samples (urine sampling) (Peaston and Weinkove, 2004). In population samples the focus will usually be on baseline levels, although stress-induced changes can also be measured in plasma samples under experimental conditions. Repeated release of epinephrine can damage blood vessels and arteries, increasing blood pressure and associated cardiovascular risks. Catecholamine measurement is used in the clinical diagnosis of adrenal gland or nerve tissue tumours (Low and Mathias, 2005). The normal range for epinephrine is up to 140 picograms (pg)/mL. The normal range for norepinephrine is 70 to 1700 pg/mL (Guber et al, 2021). Cortisol's status as 'the stress hormone', the shorter timeframe of effects of epinephrine, and

the ability to measure cortisol in saliva, has likely made cortisol more commonly measured in population samples. Example of use: (Cohen et al, 2006a).

## Immune system markers

The role of the immune system is to provide resistance to pathogens and toxins via mechanisms that include the production and transport of white blood cells, antibodies, and inflammatory and anti-inflammatory compounds (Institute for Quality and Efficiency in Health Care (IQWiG), 2020). The innate immune system is the body's first line of defence against pathogens and foreign bodies entering the body. It responds in a universal way regardless of the foreign body, first the protection offered by skin and mucous membranes. If this first line of defence is breached, immune system cells (leukocytes) and proteins are activated to scavenge and neutralise germs. Natural killer cells also play a role in identifying and destroying cells infected. If the innate immune system is unable to destroy the infection, the adaptive immune system is called into play. Unlike the non-specific innate response, the adaptive immune system specifically targets the infection cause. The adaptive immune system is made up of T cells, B cells and antibodies in the blood and other bodily fluids. B cells produce antibodies that attack invading foreign bodies, while T cells destroy the body's own cells that have been infected with viruses or become cancerous. Notably the immune system can also inadvertently damage the body when attempting to protect it though, as seen with autoimmune diseases such as Lupus or rheumatoid arthritis. There are interactions between this system and the circulatory, endocrine, excretory, integumentary, nervous and respiratory systems. Inflammatory markers include C-reactive protein, ferritin, fibrinogen and interleukin-6 which capture the innate immune system response.

### *C-reactive protein*

C-reactive protein (CRP) is an acute phase protein primarily produced by hepatocytes in the liver that exhibits elevated concentration in response of the body to injury (tissue damage, infectious and non-infectious diseases and trauma) and is otherwise scarcely present in the blood (Pepys and Baltz, 1983; Pepys and Hirschfield, 2003). CRP plays a variety of key roles in the immune system as a marker of inflammation. Concentration of CRP rises rapidly within a few hours after acute tissue injury or inflammation and falls rapidly afterwards. CRP levels are generally below 3 mg/L in healthy persons but can rise above 500 mg/L following an acute-phase stimulus (Mac Giollabhui et al, 2020). Multiple assays using anti-CRP antibodies, such as immunonephelometry, immunoturbidimetry, immunoluminometry and enzyme-linked immunosorbent assay (ELISA), are available allowing the detection of CRP from serum or plasma (Roberts et al, 2001). CRP has been extensively studied for association with a large number of non-infectious diseases as well as the onset and progression of a wide spectrum of diseases including atherosclerosis and coronary heart disease (Emerging Risk Factors Collaboration et al, 2010) and risk of some cancers (Allin and Nordestgaard, 2011). Additionally, prospective epidemiological studies suggest that many factors are risk factors for circulating CRP values, including demographic and socioeconomic factors (age, sex, socioeconomic position, ethnicity), dietary and behavioural factors (BMI, exercise, diet) and other medical conditions (sleep, medication use) (Kushner et al, 2006). More

specifically, systematic reviews of population-based studies reported that disadvantaged socioeconomic position in childhood and/or assessed by education was associated with elevated CRP level in adulthood (Nazmi and Victora, 2007; Liu et al, 2017). Example of use: (Berger et al, 2019).

### *Ferritin*

Ferritin is a protein with the primary role of storing iron, making it available to critical cellular process while preventing the potential toxic side-effects iron can have on other proteins, DNA and lipids (Knovich et al, 2009). It is a commonly used clinical biomarker for iron deficiency and often appears as iron deficiency anaemia, where there are low levels of red blood cells or haemoglobin in the blood (iron is a key part of red blood cells), limiting the ability to carry oxygen to the body's tissues. As well as its primary role, serum ferritin has also been identified as a marker of inflammation, although its causal role is less clear. Kell and Pretorius, for example, hypothesise that serum ferritin originates from damaged cells and both correlates with, and plays a causative role in, some inflammatory diseases such as hypertension and coronary artery disease (Kell and Pretorius, 2014).

Ferritin is typically measured from serum samples using some form of immunoassay, such as an electrochemiluminescence immunoassay (ECLIA) which utilises election-chemical luminesce (the production of light when stimulated by electricity) or an immunoturbidimetric assay which measures turbidity (cloudiness) of the sample to quantify levels. Normal ferritin levels are between 30–200ng/mL in women and 30–300ng/mL in men (Silvestre et al, 2017). As well as sex differences, ferritin has been shown increase in populations as adults age, although may be depleted in older ages (75+) (Fairweather-Tait et al, 2014; Institute for Social and Economic Research, 2022). As ferritin is a marker of inflammation, acute infections can raise levels and this should be accounted for in analyses (for example, excluding individuals with a known infection or acute injury) (WHO, 2020). Ferritin levels are also influenced by anti-inflammatory medication use (Fleming et al, 2001). Example of use: (Williams et al, 2002).

### *Fibrinogen*

Fibrinogen is a soluble glycoprotein and an important component of the coagulation cascade (blood clotting), primarily produced by liver hepatocytes (main cells in the liver) and is converted into the insoluble protein fibrin during the clotting process. Because fibrinogen is a major plasma protein, a small elevation in fibrinogen level will have a significant impact on plasma viscosity which in turn can increase thrombotic risk (when blood clots block blood vessels). Fibrinogen is also a key player in several physiological processes including inflammation and atherogenesis (atherosclerotic plaque formation leading to heart disease) (Kamath and Lip, 2003) and other diseases (Vilar et al, 2020). In addition, epidemiological studies have been accumulating convincing evidence that fibrinogen is an independent risk factor for cardiovascular disease (Fibrinogen Studies Collaboration et al, 2005). Many environmental, lifestyle and physiological risk factors have also been found associated with fibrinogen levels, such as age, gender, ethnicity, smoking, BMI, physical activity, hormonal factors, socioeconomic position and stress (Kamath and Lip, 2003).

A variety of tests and assays have been used to estimate fibrinogen concentrations based on different principles (De Maat et al, 1999). However, the recommended method is the Clauss fibrinogen assay (Mackie et al, 2003) which measures the ability of fibrinogen to form fibrin after being exposed to a high concentration of purified thrombin from plasma samples. Example of use: (Davillas et al, 2017).

*Interleukin 6 (IL-6)*

Interleukins (ILs) are a group of cytokines that play a key role in the immune system. Cytokines are proteins involved in the communication between cells of the immune system, but can also have regulatory functions in other physiological systems (Tanaka et al, 2014). There are 37 ILs, whose functions range across the immune system including immune cell activation, differentiation, growth and adhesion (Justiz Vaillant and Qurie, 2024). There is insufficient space here to examine all 37 ILs, so have focused only on IL-6, which is considered one of the most important inflammatory cytokines. It has been proposed that IL-6 is one of the major cytokines that stimulate the hypothalamic–pituitary–adrenal axis (the HPA axis) during inflammatory stress (Lyson and McCann, 1991). IL-6 is produced by a wide variety of cell types including immune cells (monocytes/macrophages, T cells, B cells and granulocytes) and also non-immune cells (fibroblasts, keratinocytes, endothelial cells, mesangial cells, glial cells, chondrocytes, osteoblasts and smooth muscle cells) (Kishimoto, 1989). Levels of IL-6 are very low under normal conditions, but these levels can raise in response to a variety of pathological states, such as inflammation, infection, wound sites, haematopoiesis and oncogenesis. Increased levels of IL-6 have been observed in autoimmune diseases but also cardio-metabolic diseases and some cancers (Maggio et al, 2006). There are several commercially available Enzyme-Linked Immuno-Sorbant Assay (ELISA)-based immunoassays to measure IL-6 concentration from serum samples (Thompson et al, 2012).

Several factors have been implicated in circulating IL-6 levels. IL-6 increases have been linked with age and body mass index (Himmerich et al, 2006), disadvantaged socioeconomic position (Muscatell et al, 2020), lower physical activity (Elosua et al, 2005) and lower yoga practice (Djalilova et al, 2019) in individuals exposed to early life adversity (Baumeister et al, 2016) and in individuals who experienced laboratory-induced psychosocial stress (Steptoe et al, 2007). Example of use: (Muscatell et al, 2018).

## Muscular system markers

The muscular system works with the circulatory, nervous and skeletal systems to produce movement and help circulate blood through body. There are also interactions with the digestive and endocrine systems. Here we consider just grip strength and lean mass as relevant markers.

*Grip strength*

Grip strength is a measure of overall muscle strength/function, which is an important predictor of disability, morbidity and mortality in later life (Bohannon, 2019). Normal values are relative to age and gender, with values typically starting to decrease from

the age of 60 (Budziareck et al, 2008). Participants grip a dynamometer three times with each hand and maximum strength (measured in kilograms) is used. Age and sex should be routinely adjusted for and some studies also adjust for height as body size is a determinant (Bohannon, 1997; Budziareck et al, 2008). Example of use: (Syddall et al, 2009).

*Lean mass*

Lean mass (or lean body mass) is a measure of the total weight of your body minus the weight that is made up of fat (fat mass). A combination of low lean mass and loss of muscle strength (for example, as measured by grip strength), have been recognised as markers of sarcopenia, the age-related loss of skeletal muscle mass and function (Cooper et al, 2013). Lower levels of lean mass are also associated with increased risks of osteoporosis, as lower lean mass is associated with decreased bone mineral density (Ho-Pham et al, 2014). Inconsistent patterns have been observed between SEP and lean mass (Bridger Staatz et al, 2021). Lean mass does differ with weight, height, sex and age, and these are typically adjusted for in analyses.

Lean mass can be estimated using techniques such as Dual-Energy X-ray Absorptiometry (DEXA or DXA) (Kiebzak et al, 2000), computerised tomography (CT) or magnetic resonance imaging. Alternatively, a less expensive, quicker and less invasive method utilised is Bioelectrical Impedance Analysis (BIA) (Sergi et al, 2017). These methods do not necessarily agree due to intra-individual factors (for example, hydration status) and it is important to use one method consistently for lean mass estimation across a single study (Rodriguez-Sanchez and Galloway, 2015).

The most common measure used is DEXA, whereby participant lies horizontal on a bed while being scanned by the DEXA machine, akin to a whole-body x-ray (although the radiation exposure is much lower than that of an x-ray). The x-rays used contain two, distinct energy peaks, one absorbed mainly by soft tissue and the other peak absorbed by bone. This then allows the lean mass value to be estimated. Example of use: (Guo et al, 2018).

For BIA, a weak and safe electric current is passed through the body. BIA devices may be designed to be held, stood on or may use electrodes attached to, for example, the arms and legs. Voltage is measured to calculate impedance (resistance) of the body. The electrical signal passes freely through the bodily fluids found in lean tissue, but encounters resistance when it tries to pass through fat tissue (Khalil et al, 2014). During measurement temperature can alter results so should be kept within a consistent range (Sergi et al, 2017). Hydration status is also an important consideration when using BIA for serial assessment of lean mass (Ugras, 2020). Example of use: (Bann et al, 2014).

## Respiratory markers

The respiratory system is responsible for providing the body with oxygen and to remove carbon dioxide, with the lungs the major organs involved in these processes. The respiratory system interacts directly with the circulatory system, but also more indirectly with the immune system and the nervous system. Markers include forced expiratory volume, forced vital capacity, oxygen saturation and peak flow rate.

*Forced expiratory volume (FEV1)*

Forced expiratory volume (FEV) measures how much air a person can exhale during a forced breath. The amount of air exhaled may be measured during the first ($FEV_1$), second ($FEV_2$) and/or third second ($FEV_3$) of the forced breath. $FEV_1$ is the most used marker and shows various airway abnormalities and obstruction, for example, chronic obstructive pulmonary disease (COPD) and asthma. Results from pulmonary function testing are typically combined with forced vital capacity (FVC) and the ratio FEV1/FVC is calculated. It can also be used to grade asthma severity. Normal values can vary with age, height, weight, gender and ethnicity (Borg et al, 2014). Typically, the highest value is taken from 3–5 samples per individual. Example of use: (Gray et al, 2013).

*Forced vital capacity (FVC)*

FVC highlights various airway abnormalities and obstruction, for example, COPD and asthma. Results from pulmonary function testing are typically combined with forced expiratory volume (FEV1) and the ratio FEV1/FVC is calculated. A pulmonary function test (PFT) measures FVC in millilitres. Normal values can vary with age, height, weight, gender and ethnicity (Borg et al, 2014). Typically, the highest value is taken from 3–5 samples per individual. Example of use: (Gray et al, 2013).

*Oxygen saturation*

Oxygen saturation ($SpO_2$) is a measure of how much haemoglobin in the blood is bound to oxygen, compared to how much haemoglobin is unbound. A pulse oximeter is a non-invasive device placed over a person's finger which measures light wavelengths to determine the ratio of the current levels of oxygenated haemoglobin to deoxygenated haemoglobin (Hafen and Sharma, 2021). A normal value is 95% or above. Values below 95% are indicative of hypoxia, where not enough oxygen makes it to the cells and tissues in the body. This can cause mild problems such as headaches and shortness of breath or in severe cases it can negatively affect heart and brain function. Example of use: (Friedman et al, 2020).

*Peak flow rate*

Peak flow rate measures the maximum rate of forced expiration of air from the lungs. Measurement is used for identifying patients with asthma, where rates below 80% of published guidelines are considered indicators of asthma. Previously this measure may have been used instead of FEV1 due to the easier measurement (using a peak flow meter), although now spirometers are cheap and relatively easy to include in large-scale surveys. Measured in litres/minute, with normal values ranging from 400 to 700 litres/minute. Normal values vary with age, height, gender and ethnicity (Haas et al, 2012). Typically, the highest value is taken from three samples per individual. Example of use: (Haas et al, 2012).

## Cross-system/composite markers

Some biomarkers are not associated with one specific (or primary) physiological system and some biological concepts require measures across physiological systems.

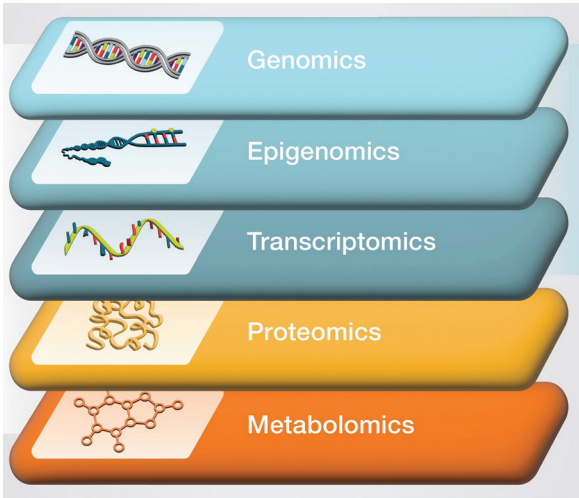
As already highlighted, every physiological system interacts with at least one other and, if we want to understand the impact that the social environment can have on physiological function and health, markers across physiological systems or composite scores incorporating multiple biomarkers, can provide additional insights. In this section we outline some key cross-system concepts/measures, following starting with omics cascade, moving from genomics to epigenomics, followed in turn by transcriptomics, proteomics and then metabolomics (Figure 1). We then move to measures further downstream that highlight physiological dysregulation (allostatic load), biological and epigenetic ageing, and then finishing with anthropometric measures which capture the body from outwith the blood, cells, tissues and organs.

### *Genomics*

Genomics broadly refers to the study of genomes. The human genome contains 3.2 billion nucleotide 'base pairs' that are bonded together and stored in cells as DNA (deoxyribonucleic acid) packaged in (for most people) 23 pairs of chromosomes. There are four bases which form specific pairings: adenine (A) with thymine (T), and cytosine (C) with guanine (G). Humans are diploid organisms, so at any given point in the genome they have two copies of the genetic code: one inherited from the mother and one inherited from the father. Human genomes differ at around 20 million of these pairs (Auton et al, 2015), with these sites of variation referred to as single nucleotide polymorphisms (SNPs). Where genotypes differ at a specific base pair throughout a species, the variations are referred to as alleles. Humans can therefore carry either zero, one or two copies of a specific allele.

DNA is used as a template by RNA (ribonucleic acid) to make proteins, via the processes of transcription and translation. During transcription, an enzyme of RNA polymerase reads a single strand of DNA and copies the information to messenger RNA (mRNA), substituting thymine for uracil (U). This produces mRNA which is a

**Figure 1:** Omics cascade




*Source:* ThermoFisher Scientific (2022).

single-stranded copy of DNA. During translation, this single strand of mRNA is read by ribosomes to produce a particular amino acid chain which forms a protein. Amino acids are determined by specific sequences of three bases, referred to as a codon. Only a small amount of DNA codes for amino acids (referred to as 'coding DNA'), with 98% of human DNA not coding for protein sequences (referred to as 'non-coding DNA'). Single genes can be important for a very small number of specific conditions, such as cystic fibrosis and Huntington's disease, but provide less useful information on diseases such as heart disease, diabetes and so on (West-Eberhard, 2008). Where data on single genes can be more valuable is when utilising them as a methodological tool such as with Mendelian Randomisation (MR). MR is an analytical method that uses genetic variants as a form of instrumental variable (IV) analysis, employed to estimate the causal relationship between an exposure and an outcome. In MR, these genetic variants act as proxies for the exposure and have been used to test reverse causation in social epidemiological studies, for example (Harrison et al, 2020). MR (and IV more generally) is a valuable tool when controlled experiments are not feasible and benefit from reduced confounding and reverse causation risks (Smith, 2010).

*Genome wide association studies*

The mainstay of genomic analyses is genome wide association studies (GWAS), which aim to identify how SNPs associate with an outcome (phenotype) of interest and the strength of these associations. Because of the size of the human genome, a single GWAS can estimate millions of associations (one for each measured SNP). Stringent p-value thresholds are therefore used to reduce the likelihood of false positive discoveries because of multiple testing, with a common *genome-wide significance* threshold of $p=5x10^{-8}$ (Pe'er et al, 2008). Many human traits are typically associated with thousands of SNPs (referred to as *polygenicity*), each of which have a very small association. For example, the largest GWAS of educational attainment to date identified 3,952 SNPs that associated with years of education. Associations between SNPs and educational attainment have a small effect size (0.008 to 0.053 standard deviations) (Okbay et al, 2022). Given the presence of small effect sizes and the statistical power required to detect these, GWAS are typically conducted on very large samples with upwards of hundreds of thousands of individuals. These samples may combine data from multiple studies, the results of which are meta-analysed. GWAS results are typically interpreted to reflect biological effects of genetic variation on the phenotype of interest, but these can also reflect closely related traits or sources of bias from demographic and familial processes (Morris et al, 2020b). Reflecting the Eurocentric focus of genetic research studies globally, GWAS are predominantly conducted on samples of European ancestry (Mills and Rahal, 2019). This means that their results may not be generalisable to other populations (Martin et al, 2019). Example of use: (Lee et al, 2018).

*Polygenic scores*

While the associations of individual SNPs identified in GWAS are typically very small, when combined they can statistically explain a considerable proportion of variation in phenotypes. This combination of SNPs is referred to as a *polygenic score* (also referred to as a *polygenic index* or *polygenic risk score*) (Dudbridge, 2013; Becker

et al, 2021). Polygenic scores provide an estimate of the summed effect of all SNPs that have been identified to associate with a phenotype. As such, they provide noisy but reliable proxies for genetic predisposition (Belsky and Israel, 2014). Polygenic scores are created by weighting SNP effect sizes obtained from GWAS by the number of 'risk' or 'effect' alleles that an individual possesses for that SNP. Polygenic scores are becoming increasingly powerful; the most recent polygenic score for educational attainment, created from 1,271 independent SNPs, explains 13% of the variation in years of education, comparable to some familial, demographic and social variables (Morris et al, 2020a). Polygenic scores are also becoming more widely used in research for a variety of applications. For example, they may be used for prediction in combination with other clinical or social factors (Lewis and Vassos, 2020); to explore the role of genotype on longitudinal trends in health (Kwong et al, 2021); for causal inference (Brumpton et al, 2020); or as a means to investigate social factors under alternative assumptions to traditional social scientific work (Morris et al, 2018). Example of use: (Khera et al, 2019).

*Epigenome-wide association studies*

Epigenetics build on our knowledge of the genome to focus on changes in gene expression, the process by which the information encoded in a gene is turned into a function via transcription (DNA to RNA) and translation (RNA to protein). These epigenetic changes represent gene modifications that do not involve alterations in the DNA sequence itself. In the social-to-biological context, researchers are particularly interested in how social and environmental factors can modify gene expression, thereby potentially driving changes in the risk of developing certain diseases (Castagné et al, 2023). Epigenome-wide association studies (EWASes) can be used to examine the association between a phenotype or risk factor and epigenetic changes. These epigenetic changes include histone modifications, changes in non-coding RNA's and DNA methylation (DNAm) (O'Donnell and Meaney, 2020). DNAm is by far the most common mechanism investigated and refers to the addition or removal of methyl (-CH3) groups to Cytosine-phosphate-Guanine (CpG) sites of the genome (Campagna et al, 2021). DNAm is important for gene regulation and gene expression, and a high level of DNAm in gene promoters is generally associated with transcriptional repression (that is, gene silencing) (Champagne, 2010). The most common way to study DNAm is with bisulphite converted genomic DNA and microarrays (Campagna et al, 2021). Like GWAS, EWAS generally require large sample sizes to detect differences, with complex phenotypes typically having effect sizes of 5% or less (Campagna et al, 2021). The statistical association between methylation levels and phenotypes of interest can be pinpointed at the level of individual CpG sites or genomic regions (for example, see Epigenetic clocks section). An important difference from GWAS is that EWAS is highly variable depending on the cell type studied and changes over time, which makes its use even more complex. Example of use: (Alfano et al, 2019).

*Transcriptomics*

Transcriptomics can be defined as the study of transcriptomes and their function. The transcriptome includes all RNA molecules (also known as transcripts) found

in a cell or in population of cells (Srivastava et al, 2019). RNA strands encode information copied from DNA during transcription. In addition to the protein-coding messenger RNA (mRNA), the transcriptome includes non-coding RNAs such as microRNA (miRNA) or long non-coding RNA (lncRNA) that contribute to various structural and regulatory functions in cells (Mattick, 2011). The most common modern transcriptomic methods are microarrays and RNA-Sequencing (RNA-Seq). Microarrays quantify a predefined set of sequences (Bumgarner, 2013), whereas RNA-Seq captures all sequences (Lowe et al, 2017). Transcriptomics requires a complex set of skills given the diversity of the steps involved in the process from sample processing and molecule extraction to the bioinformatic curation and synthesis of the results. It should be noted that the transcriptome is dynamic (Srivastava et al, 2019) and RNA expression could vary depending on the cell examined (for example, blood cell versus skin) or the timing of the analysis (that is, the expression of an RNA could be different before a condition develops compared to expression after it developed). Analysing and comparing transcriptomes from different cells/tissues generates a holistic understanding of cellular functions, facilitates disease diagnosis and profiling, and contributes to the investigation of molecular mechanisms underlying different phenotypes. Example of use: (Castagné et al, 2016).

*Proteomics*

The proteome is the collection of proteins produced or modified by a cell or tissue. Proteomics methods identify and quantify proteins as well as protein interactions in cells and tissues (Graves and Haystead, 2002). Transcriptomics can indicate protein expression by examining mRNA expression (see Transcriptomics section). However, studying only the protein-coding messenger RNA (mRNA) does not account for processes involved in translation (mRNA to protein) like post-translational modifications that can play important roles in cellular functions. Therefore, dedicated methods are needed to assess the proteome. Protein microarrays, affinity chromatography, nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are among the techniques that can be used to analyse protein structure, behaviour and interactions (Shah and Misra, 2011; Aslam et al, 2017). The sensitivity and specificity of MS makes it a method of choice in proteomics. MS relies on measuring what is known as the 'mass-to-charge ratio' of ionised proteins, which essentially allows different molecules in a sample to be separated and plotted in the form of a histogram called a 'mass spectrum' (Chandramouli and Qian, 2009). A well-designed proteomics study offers an in-depth overview of cellular biological and physiological status given that proteins have a significant influence on the cellular microenvironment. Like other omics techniques, proteomics requires a versatile skillset covering sample preparation (for example, protein extraction, processing) to data synthesis (for example, bioinformatic techniques). When using proteomics, it is essential to understand that the proteome is constantly changing based on the biological needs of the organism (Beynon, 2005). Consequently, proteome profiles represent a snapshot of the proteome, and past or future protein levels or modifications cannot be examined. Proteomic studies have been used to facilitate understanding of the physiological and pharmacological role of proteins in biological systems, leading to the discovery of biomarkers for different conditions as well as new drugs and therapies. Example of use: (Ubaida-Mohien et al, 2019).

*Metabolomics*

Metabolomics is an analytical technique used to study the metabolome – all metabolites and their interaction within a biological system. A metabolite is a small molecule (that is, peptide, lipid, oligonucleotide, sugar, amino acid, toxin, and so on) that contributes to, or results from, metabolic reactions in a cell or tissue (Hollywood et al, 2006). The concentration of metabolites is highly variable; small molecules are constantly degraded, absorbed, or synthesised in normal and abnormal physiology. The most popular techniques in metabolomics studies are mass spectrometry (MS) and nuclear magnetic resonance (NMR). The former method was previously described (see Proteomics section), while the latter involves sample exposure to a magnetic field and radiofrequency pulse. Energy absorbed and re-emitted by chemical nuclei allows the quantification of metabolites (Emwas, 2015). NMR has high reproducibility and requires minimal sample preparation but is not optimal for targeted analysis. MS is more appropriate for targeted analysis, but sample preparation is more complex and more time-consuming (Emwas, 2015). Like other omics techniques, the skillset involved is highly specialised. Current techniques generate an instantaneous snapshot of the metabolome, but the metabolome is highly volatile. However, this volatility is also an advantage that can be used to assess sudden biochemical changes following a stimulus/exposure. Metabolic profiling is beneficial for a variety of disciplines as it provides a vivid description of the physiological state of a cell or tissue (Hollywood et al, 2006). Metabolomics has many uses including profiling disease (for example, by analysing the concentration of relevant metabolites in blood or urine) and assessing drug safety or developing personalised treatment strategies (Dunn et al, 2010). Examples of use: (Robinson et al, 2021).

*Allostatic load*

Allostasis refers to the process of adaptation to acute stress, involving the output of stress hormones and a physiological cascade which acts to restore the body's physiological systems to homeostasis (stable level of function) in the face of some kind of endogenous or exogenous challenge/stressor (Sterling and Eyer, 1988). Allostatic load refers to the 'price' the body pays for having to adapt to these challenges/stressors, and as such it constitutes either the presence of too much stress or the inefficient operation of the stress hormone response system (McEwen, 2000). Measuring allostasis in humans is difficult as it is a process that is happening so often in the body. However, McEwen (who brought the concept into focus in the late 1990s/early 2000s) and colleagues proposed a measure that might capture allostatic load and the physiological response to stress by combining measures across multiple physiological systems, thereby measuring this 'load' or so-called 'wear and tear' on the body. As a measure, allostatic load is constructed as a composite score based on combining biomarkers across the cardiovascular, metabolic, immune and neuroendocrine systems (McEwen and Seeman, 1999). Commonly, the allostatic load score will include measures such as blood pressure, cholesterol and C-reactive protein in its calculation (in combination with other markers). Higher scores indicate greater physiological wear and tear and have been shown to predict morbidity like cardiovascular disease, cognitive and physical performance (Seeman et al, 2001), subjective health (Hu et al, 2007; Barboza Solís et al, 2016) and all-cause mortality (providing better prediction as a composite score rather than the

individual biomarkers) (Parker et al, 2022). A key issue with the measure is that there is no consistent and agreed upon construct in terms of both the biomarkers to include and how to compute the score, with researchers using methods such as clinical cut-points, quartiles/deciles of risk, z-scores and/or factor analysis (Juster et al, 2010; Delpierre et al, 2016). A recent study, analysing data for over 60,000 individuals aged 40–111 years participating in 13 different cohort studies and utilising 40 biomarkers across 12 physiological systems, has identified a five-item measure of allostatic load that could provide a step towards a consistent, validated measure (McCrory et al, 2023). Despite these issues with consistency, though, there does appear to be reliable evidence for a social patterning of allostatic load, with higher scores associated with lower socioeconomic position (SEP) (Johnson et al, 2017), as well as other important stratification factors like gender, age and race/ethnicity (Rodriguez et al, 2019). Example of use: (Robertson et al, 2015).

### *Biological ageing*

Biological ageing is the incremental, universal and intrinsic degeneration of physical and cognitive functioning and the ability of the body to meet the physiological demands that occur with increasing chronological age (Adams and White, 2004; Robertson et al, 2013), which are not always well correlated, suggesting that they measure different phenomena. Here we explore some of the most widely used ones.

#### *Telomere length*

Telomeres are non-coding pieces of DNA present at the ends of chromosomes and are important in protecting the 'functional' part of the chromosomes from deteriorating or fusing with other chromosomes during cell division. With each cell division telomeres are shortened and eventually they no longer protect the chromosome. This can result in DNA damage or cellular senescence, where senescent cells stop multiplying but do not die. Instead they continue to release chemicals that can trigger inflammation and damage nearby, healthy cells (Hernandez-Segura et al, 2018). Longer telomere lengths have been associated with longer years of life lived and varying problems in telomere length are implicated in cancers, cardiovascular disease, neurological issues, immunodeficiencies, structural malformations and increased rates of DNA damage (Cawthon et al, 2003; Lai et al, 2018). Shortened telomeres are associated with increased chronological age, but there is enough variation between individuals (due to the variety of exposures experienced by individuals/groups) that they allow for an estimate of biological age (Der et al, 2012). There have been a number of methods used for measuring telomere length, with the most common being terminal restriction fragment (TRF)/southern blot and polymerase chain reaction techniques (such as qPCR) (Montpetit et al, 2014; Lai et al, 2018). Each method has its strengths and weaknesses, but in general TRF techniques have good reproducibility (qPCR less-so) and provide a measured 'length' (qPCR provides a relative telomere length compared to a reference). However, TRF techniques are more expensive, require larger amounts of starting DNA, are more labour-intensive and therefore can be difficult to use in large-scale studies (Martin-Ruiz et al, 2014; Lai et al, 2018). Example of use: (Robertson et al, 2013).

*Klemera and Doubal physiological age*

First developed by Petr Klemera and Stanislav Doubal, 'KD' physiological age uses a mathematical algorithm to calculate what they propose is an optimum method of estimating biological age (Klemera and Doubal, 2006). This process is complex and involves using multiple ageing biomarkers and individually regressing each biomarker on chronological age, before using the estimated coefficients from each linear regression as new weights (rather than using chronological age) for a final regression model testing the combined measure. This technique was developed as a method for overcoming flaws when using multiple linear regression, however its complexity has meant it is not commonly used, and when utilised is typically compared to other measures of biological ageing. In these analyses, the KD method does perform well as an estimate of biological age, especially in relation to predicting mortality (Levine, 2013). The biomarkers included in the modelling are not explicit to the KD method, but are suggested by researchers, often with strong theoretical reasons for inclusion as ageing markers. The modelling itself can be used to identify measures that can be removed from the final model if they do not perform well in the initial modelling. Markers used have included CRP, creatinine, HbA1c, sBP, total cholesterol and FEV1, all of which have been described earlier in this article. Example of use: (Levine and Crimmins, 2014).

*Epigenetic clocks*

Primary 'hallmarks of ageing' include telomere erosion and epigenetic modifications, particularly DNAm (see section on Epigenome-wide association studies) (López-Otín et al, 2013). There are ~28 million CpG sites in the human genome and it is estimated that the methylation states of approximately one third of these sites change with age, both positively and negatively (Horvath and Raj, 2018). Importantly, DNAm is modulated by lifestyle and environmental factors, and represents a candidate mechanism for the biological embodiment of social exposures across the life course (McCrory et al, 2019).

The advent of machine array technology, coupled with advances in machine learning (for example, elastic net), allowed for the identification of a subset of CpG sites that could be used to estimate the age of the DNAm source. Early studies showed that the correlation of DNAm age with chronological age was in the region of 0.95 in samples with a full age range (Horvath and Raj, 2018). The regression of DNAm age on chronological age was hypothesised to provide an index of the biological ageing rate, with a positive/negative residual signifying someone ageing faster/slower than their chronological age, hence the name, epigenetic clock. Importantly, these clocks have been shown to predict mortality independently of chronological age (Oblak et al, 2021). Some recent (pre-print) evidence does caution the use of these clocks though, with accumulating stochastic variation able to accurately predict chronological and biological age and positing that the current ageing clocks could simply be picking up random alterations in methylation (Meyer and Schumacher, 2024).

There are now a large number of epigenetic clocks in existence based on levels of DNAm at a subset of sites, ranging between 3 and 1030 CpG's (Bergsma and Rogaeva, 2020). The latest release of data from the American Health and

Retirement Study (HRS) includes data for 13 epigenetic clocks (Crimmins et al, 2021), although Hannum, Horvath, PhenoAge and GrimAge tend to be those most heavily used in social science research at present (and briefly described in what follows). There is a distinction made in the literature between what has been termed the first- and second-generation epigenetic clocks. The first-generation clocks (for example, Horvath and Hannum) were designed to be highly accurate predictors of chronological age and measure changes in DNAm shared between individuals. The second-generation clocks (for example, PhenoAge and GrimAge) by contrast were designed to gauge inter-individual variability in the pace of ageing and were trained using clinical biomarkers in addition to chronological age. Recent studies have shown that the second-generation clocks are more strongly associated with SEP (George et al, 2021), lifestyle factors (Fiorito et al, 2019), age-related clinical phenotypes, and mortality (McCrory et al, 2021) compared with their progenitors, although may yet not be as strongly linked with the likes of SEP as other cross-system markers like allostatic load (McCrory et al, 2019). Example of use: (Oblak et al, 2021).

*Horvath clock*

DNAm at 353 CpG loci associated with chronological age using multiple DNAm datasets encompassing 51 different non-cancerous tissue and cell types. Published in 2013 and then updated using additional samples in 2018 (Horvath, 2013).

*Hannum clock*

DNAm at 71 CpG sites associated with chronological age in whole blood samples, originally from two US cohorts (n=482) (Hannum et al, 2013).

*PhenoAge clock*

DNAm at 315 CpG loci associated with 'phenotypic age', calculated using ten measures of age (including age itself) that all are associated with and predict mortality. Original study used US data from the NHANES III (Levine et al, 2018).

*GrimAge clock*

Composite biomarker based on seven DNAm surrogates and a DNA methylation-based estimator of smoking pack-years. Adjustment for chronological age represents biological age (Lu et al, 2019).

*DunedinPace*

The DunedinPace clock is qualitatively different from other ageing clocks as it represents a rate measure (that is, how fast a person is ageing) compared with a state measure (that is, how much ageing has occurred up to that point) and was developed by identifying DNAm correlates (173 CpG sites) at a single time point of decline in 19 indicators of organ-system integrity across four measurement occasions spanning two decades (Belsky et al, 2022).

*Anthropometric markers*

Finally, we describe some concepts and measures that do not easily fit into the cross-system grouping as they measure the size, shape and composition of the human body and have been well-researched for their links with health outcomes (and social circumstances).

*Body mass index*

The most widely used measure for classifying obesity is the body mass index (BMI), which is calculated by dividing body weight (in kilograms) by height (in meters) squared. There are a variety of cut-points for using the BMI to classify people as underweight, normal weight, overweight or obese, although typically 18.5 is underweight, 18.5–24.9 normal, 25–29.9 overweight and 30 or more indicates obesity (Hruby and Hu, 2015). BMI is widely used as it is easy to measure (simple, inexpensive and non-invasive), its widespread use allows easy comparisons at the population level and, over time, it takes stature into account when calculating obesity and it correlates well with percentage body fat and future health risks. It does have its weaknesses, though, as it is a measure of excess weight rather than excess body fat, per se. For example, people with high muscle mass will also have high BMIs. In addition, some ethnic groups may have higher risks associated with lower BMI values than cut-offs suggest. Example of use: (Hoebel et al, 2019).

In addition to increasing total body weight being associated with greater risks to health, more fat in the abdomen or trunk has been associated with increased health risks (Balkau et al, 2007). This 'central' or abdominal obesity can be measured through MRI scans, but it is typically measured as waist circumference (WC) or waist-to-hip ratio (WHR).

*Waist circumference*

Waist circumference (WC) can be measured in several places using a tape measure. Many studies favour using the tip of the hip bone for consistency, with the tape measure going over the navel. However, WC can also be measured at the narrowest part of the midriff or just below the bottom rib. The International Diabetes Federation typically suggests a cut-off of 80cm in women and 90cm in men if defining obesity (Alberti et al, 2007). Example of use: (Zaninotto and Lassale, 2019).

*Waist-to-hip ratio*

Waist-to-hip ratio (WHR), like WC, requires a tape measure to measure the circumference around the waist and the hips. The waist is measured as with WC and usually the hips are measured at the widest circumference around the buttocks. The WHR cut-off points to detect obesity are ≥1.0 and ≥0.85 for males and females, respectively (World Health Organization, 2011). Example of use: (Shahraki et al, 2008).

Harvard health detail the pros and cons of using WC and WHR (Measuring how fat we are, 2009). Both WC and WHR are relatively easy to measure (only requires a tape measure, inexpensive and non-invasive). Although not as common as BMI, they are both still widely used (especially in surveys and cohort studies)

which can allow for relatively easy comparisons at the population level and over time. WC is a good indicator of fat in the abdominal area and a better predictor of some conditions like Type 2 diabetes compared to BMI. In turn, WHR may be a better predictor of some conditions like heart disease, than WC or BMI. WHR is a good proxy for subcutaneous fat (although the value of this is contested when it comes to this type of fat and its health effects). In terms of negatives, both WC and WHR can be measured differently by different people (for example, where on the abdomen you put the tape measure) and can lead to poor comparability with repeat measures in an individual if not measured in same place every time. ISAK training and guidelines can be used to minimise such variation though (ISAK, 2022). Cut points may be underestimating the risks of lower values and people may be less willing to allow for these measures compared to height and weight to calculate BMI.

## Concluding remarks

If we are to build interdisciplinary research capacity and improve the types and quality of research that combines social and biological data, non-biologists need to feel confident in using biological data (and vice versa with biologists using social data). There are many barriers to researchers who want to include biomarkers in their studies. Further training, networking, collaborations and open discussions on the use and misuse of such data are all key if we are to advance research in this area, to better understand the biological embodiment of our social experiences and posit, test and implement policies and practices that benefit society.

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**Conflict of interest**

The authors declare that there is no conflict of interest.

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