Race and medicine in light of the new mechanistic philosophy of science

Abstract

Racial disparities in health outcomes have recently become a flashpoint in the debate about the value of race as a biological concept. What role, if any, race has in the etiology of disease is a philosophically and scientifically contested topic. In this article, I expand on the insights of the new mechanistic philosophy of science to defend a mechanism discovery approach to investigating epidemiological racial disparities. The mechanism discovery approach has explanatory virtues lacking in the populational approach typically employed in the study of race and biomedicine. The explanatory constraints that form an integral part of the new mechanistic approach enable mechanism discovery to avoid the epistemic and normative shortcomings of the populational approach. The methodology of mechanism discovery can fruitfully be extended to the treatment and reversal of epidemiological racial disparities.

Keywords Mechanism. Race. Epigenetics. Explanation. Disease. Epidemiology

Introduction

Researching the sources of and potential solutions to epidemiological racial disparities, which are differences in rates of disease between self-described races, poses two challenges. On the one hand, critics of race-based studies argue that the continued incorporation of racial categories as proxies of genetic diversity reinforces the legacy of scientific racism. On the other hand, racial disparities in a number of biomedical outcomes, such as Alzheimer's disease, chronic kidney disease, and low birth weights, suggest that race remains a significant factor for understanding and potentially reversing epidemiological disparities between different racial populations in the United

States, and therefore "race-based studies" are an essential component of research into these disparities (Lorusso and Bacchini 2015).

Nevertheless, both advocates and critics of the race-based studies take for granted their principal mode of reasoning and investigation, namely statistical reasoning and the tools of population genetics. Whether it is in biomedical research or social science, it is statistical reasoning, the kind employed in population genetics, that is used to build evidence for hypotheses relating to racial disparities. It is "statistical evidence of associations between variables" that is prized by the statistical reasoning approach (Matthews 2017, 1006).

This paper argues that the populational/genetics approach, which remains the preeminent approach to investigating epidemiological racial disparities[1] (ERDs), has a number of epistemic and normative shortcomings. I outline the three main varieties of explanations of ERDs, which I call the racism-based explanations, genetics-based explanations, and embodiment-based explanations, and illustrate each with an example case. I argue that the dominant approach of race-based studies into ERDs, which often fall under genetics-based explanations, violate two explanatory constraints highlighted by what I call the granularity and reification problems. As I show, the granularity and reification problems pose an explanatory challenge to the prominent methodology of race-based studies of epidemiological racial disparities. This challenge stems from an inherent limitation of the populational/genetics approach in determining which variety of explanation, and subsequently what type of mechanism, is adequate.

[1] By epidemiological racial disparities I mean statistically significant differences in the incidence of disease between racialized groups. Except when discussing the views of others, I use "race" and "racialized group" interchangeably. However, see Hochman (2019) for the argument that since racialization theory is not committed to a racial ontology, "racialized groups" are conceptually distinct from "races." Since I am not committed to a racial ontology in my use of "race" (unless I am referring to another author's conception), I do not take this distinction to be a problem for my usage. Thanks to an anonymous reviewer for drawing my attention to this issue.

The main aim of this paper is to argue that there is a neglected approach to investigating and building evidence for explanations that can fruitfully be applied to research in ERDs. According to a prominent account of scientific explanation, the new mechanistic philosophy of science, successful biological explanation of a phenomenon involves describing the mechanism that produces the phenomenon. The new mechanist approach, most prominently advanced by Machamer, Darden and Craver (MDC) (2000), was initially developed by reasoning about cases from molecular biology and neuroscience. It has since been expanded as an approach to explanation throughout the life sciences and is applied to a wide range of social sciences such as economics and sociology. In his influential contribution to philosophy of biology, Tabery (2014) drew a distinction between *variation-partitioning* and *mechanism-elucidation* approaches to studying the relationship between genetics and human behavior. Variation-partitioning approaches seek to explain variation in a population by identifying causes of variation and *how much* variation each cause contributes. Their methodology is statistical. Mechanism-elucidation approaches, on the other hand, seek to explain *how* a given developmental process gives rise to a phenomenon by elucidating a causal mechanism. Their methodology is interventionist (Tabery 2014, 37). I defend a mechanism discovery approach that applies the distinct mechanistic reasoning and explanatory strategy described by Tabery (2014) and Matthews (2017) to cases of epidemiological racial disparities. The versatility of the new mechanist approach makes it an attractive candidate for investigating ERDs where there is often an interaction of several factors from the genetic to the social.

I draw on Craver and Darden's (2013) strategies for creating, evaluating, and revising mechanism schemas. This approach, which I call the *Mechanism Discovery Approach* (MDA), seeks to be guided by the nature of the phenomenon in question to discover the mechanism that produced it. I argue that the *Mechanism Discovery Approach* (MDA) provides heretofore neglected philosophical tools for explanations of ERDs. MDA goes beyond the statistical approach by showing *how*

particular disparities come to be through description of the mechanism that produced them. MDA avoids the pitfalls of race-based studies by accounting for the role of racism in mechanisms producing racial disparities.

Furthermore, this paper expands the new mechanistic philosophy of science by developing an account of activities I call *productive difference-making.* Activities as productive difference-makers satisfy the explanatory desiderata of avoiding the granularity and reification problems. This paper therefore adds to the new mechanist literature by extending the activities concept while applying it in developing an explanatorily attractive approach to investigating epidemiological racial disparities. To develop my argument with a case, I focus on the well-characterized disparity between birth weights of black and white Americans. I argue that *mechanism discovery* guides the process of scientific discovery in a direction that enables identification of the correct explanation strategy.

This paper does not defend a metaphysical view of race. However, I argue the approach I defend offers resources for proponents of both an anti-realist and race realist views of race. For the purposes of this paper, I assume that black or African American, white, Asian, etc. are racialized groups and my use of "race" refers to these racialized groups and their members. Racialization, which differs from one society to another, is a historical process of assigning individuals to different groups based on real or imagined phenotypic traits and differentially treating them in legal, political, economic, and medical spheres. This characterization might not be satisfactory for the genetic race realist, who holds that racial groups are continental populations and a proxy for human genetic diversity. But one aim of this paper is to show that research into social determinants of health shows the salience of racism, and its contingent history, to the development of disparities in multiple epidemiological outcomes.

Furthermore, I do not claim that racial classification is never useful in "researching, diagnosing, or treating genetic disorders." Rather, I highlight the normative and epistemic pitfalls of a primarily populational/genetics approach to investigating epistemological racial disparities. For instance, Spencer (2018) defends the usefulness of races understood as continental human populations in identifying "medically useful genetic differentiation" (Spencer 2018, 1034). He nonetheless acknowledges that "it really is a dilemma whether we should use any racial classification in a genetic way in medicine" (1034). Among some of the epistemic pitfalls is it may lead researchers to overlook social factors that have a better explanatory fit. A normative pitfall is that, as research has shown, reading about genetic diseases using racial categories raises the probability that one develops essentialist racial views, which typically leads to developing racist attitudes (Spencer 2018, 1034).

In contrast to the populational approach, I argue that a mechanistic approach best satisfies the normative and epistemic constraints in investigating and potentially reversing epidemiological racial disparities. What the new mechanistic philosophy of science offers is a set of in-built epistemic norms that "guide and constrain the search for a mechanism's salient features" (Darden et al., 2018b). The mechanistic constraints are much more robust than the populational approach, which often involves identifying genetic variants associated with a disease phenotype while black boxing the productive continuity between the two. This is because a mechanistic approach prioritizes discovery of causal mechanisms (with productive continuity from putative causal start-up conditions to the disease phenomenon) over causes of variation.

The paper goes as follows. First, I outline the three main explanatory approaches to ERDs and illustrates them with an example case; I also expand the critique of the most common type of race-based studies, namely genetics-based explanations, by highlighting the granularity and

reification problems. Second, I outline an account of the new mechanistic philosophy of science and briefly develop my account of activities as productive difference-makers. Third, I apply the new mechanist approach to research on racial disparities on birth weight and highlight the virtues of this approach. I conclude with a discussion of the diverse applications of mechanism discovery in philosophy and medicine.

Race and biomedicine: two approaches

In the United States, there are a number of significant epidemiological racial disparities. African Americans are two to three times more likely than whites to develop chronic kidney disease (CKD) (Tarver-Carr et al. 2002), are twice as likely as whites to develop Alzheimer's disease (Alzheimer's Association 2019, 333), and have higher rates of mortality from heart disease, strokes, and breast cancer, among other complex trait diseases (Goosby and Heidbrink 2013). These disparities are the subject of growing research at the intersection of race and medicine. Perhaps the most famous recent example of this is the development of BiDil, a drug approved by the US Food and Drug Administration (FDA) to treat heart failure in African American patients (Temple and Stockbridge 2007).

There are three broad explanatory categories of research into ERDs: genetics-based explanations, racism-based explanations, and embodiment-based explanations. Genetics-based explanations take the principal causal factor in the development of ERDs to be genetic differences between racial populations. A candidate case is research in racial disparities in Alzheimer's disease (AD) discussed below. Racism-based explanations draw from the burgeoning work on social determinants of health to explain ERDs in terms of the differential exposure of racial minorities to harmful social and environmental factors, such as discrimination, stress, poverty, inadequate

housing, and so on. I discuss the case of ERDs in asthma to illustrate this approach. Embodiment-based explanations show how socially determined health outcomes can become embodied in complex biological, though not genetic, mechanisms. Unlike in cases where racism-based models are explanatorily adequate, these embodied disease mechanisms perpetuate ERDs even in situations where proxies for racism—discrimination, poverty, inequality of health access, etc.—have been controlled for (i.e., are not a difference-maker between the target racialized groups under study). Embodiment-based explanations appeal to cases where racism's effects come to be literally embodied in racialized groups and individuals (Gravlee 2009; Sullivan 2013; Kaplan 2014). As an illustrative example of embodiment, I discuss disparities in incidence of low birth weights between white and African Americans. These explanatory strategies are not necessarily exclusive, and each has a place in research into ERDs. However, I argue the choice of which explanation is successful is best guided by a mechanism discovery approach.

Lorusso and Bacchini (2015) examine two prominent approaches taken in epidemiology and biomedical research into these disparities, which they call "race-based" and "race-neutral studies" (Lorusso and Bacchini 2015, 56). Race-based studies consider race a relevant variable in the etiology of complex diseases. The most common way race is taken up as a variable in the study design of race-based studies is as a proxy for a causally relevant factor in the production of the disease phenomenon. Usually, this causal factor is taken by many race-based studies to be *genetic,* and race therefore plays the role of proxy for genetic diversity. Lorusso and Bacchini (2015) highlight this "genetic hypothesis", which holds that "differences in the risk of complex diseases among racial groups are largely due to genetic differences covarying with genetic ancestry which self-identified races are supposed to be good proxies for" (Lorusso and Bacchini 2015, 57). Lewontin (1972) sparked an ongoing debate on whether races conceived as continental populations capture the structure of human genetic diversity with philosophers weighing in for (Sesardic 2010; Spencer

2015) and against (Andreasen 2004; Kaplan and Winther 2013) the genetic hypothesis. Lorusso and Bacchini (2015) argue that using self-identified races as a proxy for genetic diversity is both scientifically suspect and frequently obscures the real role played by racialization in fostering epidemiological racial disparities, namely the role of racism in differential exposure of different self-identified races to environmental and social determinants of health such as pollution, poverty, lack of education, and poor health care.

As I show below, the concerns about race-based studies are grounded in reasonable worries about reifying race as a genetic concept[2]. The focus of research resources on finding genetic differences to explain ERDs may also engender neglect of factors that actually make a difference to ERDs. Genetics-based explanations of disease risk are nonetheless sometimes fruitfully expanded to incorporate race (as a proxy of genetic diversity) as a potential risk factor. An illustrative case of this is Alzheimer's disease (AD). There is a robust association between the *APOE4* gene and increased risk for cognitive decline. Apolipoprotein E4 (apoE4) is present in more than half of AD patients, making *APOE4* "the most prevalent genetic risk factor for AD" (Safieh et al. 2019). *APOE4* is one of three isomorphs of the *APOE* gene, which carries instructions for the synthesis of apolipoprotein E (apoE), an important protein in lipid metabolism and transport. The apoE4 protein, unlike the more common apoE3 variant, is less effective at catabolizing cholesterol, potentially contributing to pathological buildup of cholesterol in the brain (Safieh et al. 2019).

The initial association between *APOE4* and AD was established within white populations. But the higher incidence of *APOE4* among African Americans suggested a genetics-based explanation of the significantly higher rates of AD among African Americans (Barnes and Bennett 2015). Race-based studies into ERDs in the rate of AD have also uncovered a strong association between AD

[2] Sesardic (2010) defends genetic race realism and race as a genetic concept. See Taylor (2011) for a response.

and other variants of genes involved in lipid metabolism, such as the ATP-binding cassette transporter (ABCA7), that are expressed in higher rates among African Americans (Reitz et al. 2013; Logue et al. 2014).

The upshot of the preceding discussion is that the populational/genetics approach that predominates research into AD disparities between racialized groups does not elucidate all the causally productive difference-makers and how they are organized to produce the disease phenomenon. What the populational/genetic approach provides is evidence for association between genetic factors and disease. Even when there is a well-established association between particular gene variants, such as *APOE4*, and AD risk, the relationship between genotype and phenotype in the case of complex diseases is not one of simple determination. There are a number of other genetic, comorbid, and environmental factors that determine whether possession of a gene variant associated with disease risk does in fact produce the disease phenomenon (Kaup et al. 2015). In the case of AD, education, socioeconomic status, comorbidities such as diabetes, among other factors, contribute to resilience to development of AD in individuals with high risk gene variants (Stepler and Robinson 2019). There is evidence that suggests prevalence of comorbidities is "a larger contributing factor than genetics" to AD (Stepler and Robinson 2019, 2). African Americans' lower educational attainment, higher levels of cumulative stress, and lower socioeconomic status when compared to white Americans therefore plays a significant role in AD development. Given the large number of modifiable risk factors that are associated with AD along with particular genetic variants, it is unclear whether genetics-based explanations, racism-based explanations, or embodiment-based explanations are adequate to account for ERDs in AD.

In summary, race-based studies and genetics-based explanations of ERDs reify the genetic race concept by implicitly or explicitly relying on race as a proxy for genetic diversity. Genetics-based

explanations proceed by attempting to identify associations between a gene variant that predominates within a racially-defined population and disease risk. However, even with excellent candidate cases such as AD, there are philosophical and methodological problems with how race-based studies make use of the race concept. In the context of race and biomedicine, I next outline two conceptual and scientific challenges, which I call the *granularity* and the *reification* problems, that highlight the pitfalls of a genetics-based approach that need to be avoided when engaging in race-based studies.

The granularity problem

The granularity problem faced by race-based studies reflects the difficulty in identifying just how to racially define the populations that are the relevant target for investigation and possible biomedical intervention, in the design of scientific studies and treatment protocols. As Hochman (2013) argues, following Kitcher's (2007) initial characterization of this problem, the "grain-of-resolution problem" arises because "the appropriate grain of analysis is unclear" when it comes to the number and membership of putative races (Kitcher 2007; Hochman 2013, 345). For instance, African Americans, black Caribbeans, and West Africans share recent common ancestry. The US Organization for Management and Budget's (OMB) scheme of racial classification, which is used across federal government agencies in the US (including the US census) and a large share of epidemiological studies to assess race membership, incorporates these populations as a single racial group (Black/African American) (Green et al. 2002; Spencer 2018). However, the increased mortality and morbidity of African Americans in relation to white Americans and Europeans frequently does not obtain in the case of West Africans and black Caribbeans. West Africans and recent black immigrants to the United States do not have the same higher disease risk for hypertension, low-birth weight and premature deliveries, and Alzheimer's disease, to take three

examples (Kuzawa and Sweet 2009; Valles 2012; Prince et al. 2013). Indeed, it is necessary to distinguish between white Americans and European populations (e.g., Finns) when researching diseases such as cystic fibrosis. While White Americans have a higher disease risk for cystic fibrosis compared to other racial populations in the US, Finns and Finnish migrants to the US do not (Valles 2012). The granularity problem highlights in the context of epidemiology the genetic heterogeneity within putative racial categories, raising a grain-of-analysis issue for those seeking to use "race" as a proxy for genetic diversity.

Frohlich and Potvin (2008) highlight this heterogeneity in disease risk in subpopulations in their critique of the influential "population approach" of public health research and intervention, which emphasizes maximizing harm reduction by targeting small improvements in large populations over large improvements in smaller, high-risk populations (Frohlich and Potvin 2008). The population strategy is frequently defended on grounds that it is cost-effective, as it has a single target population, and will therefore maximize the potential benefits achieved given the risks. But as Valles (2012) points out, this lumping of low-risk and high-risk populations engenders waste of resources on low-risk populations for particular diseases as a result of commitment to a dubious racial category (Valles 2012, 406).

The population approach also suffers philosophically in terms of the explanatory value of race-based research. As Root (2003) notes, race-based research in cases where there is heterogeneity of disease risk in the population substructure is explanatorily worse than alternative approaches (discussed below) since it only applies to a subset of the population (i.e., race) that these studies take to be a proxy for a causal factor in the etiology of the disease phenomenon. The more encompassing the population is (lumping), the more it ignores the heterogeneity in disease incidence among different subpopulations racialized as black. The less encompassing it is (for instance by stratifying

the target population by ethnicity, i.e., splitting), the less race can be plausibly considered a good proxy for causal factors (such as population-specific genetic variation).

The granularity problem arises in the Alzheimer's disease case discussed above (Reitz et al. 2013; Logue et al. 2014). These studies use genome wide association studies (GWAS) and whole genome sequencing (WGS) to identify specific gene variants, called single nucleotide polymorphisms (SNPs), associated with Alzheimer's disease, with race used as a proxy for genetic ancestry. These studies do not distinguish African Americans from African and black Caribbean immigrants. However, this reliance on the "genetic hypothesis" leads to a potentially serious oversight. Namely, it ignores how different populations that are racialized as black do not in fact have the same risk for developing Alzheimer's disease. Several studies of African populations have found that Africans are the least likely "continental" population-group to develop late onset Alzheimer's disease (Prince et al. 2013). Hendrie et al. (2001) found that Yoruba[3] communities in Nigeria had significantly lower rates of Alzheimer's than African American communities in Indiana (Hendrie et al. 2001). The heterogeneity in Alzheimer's disease risk cuts against the strategy of finding genetic variation between white and African Americans as a causal-explanatory factor in the difference in disease risk. The *grain* at which racialized (sub)populations are characterized can therefore significantly alter what conclusions we can draw from race-based studies. The granularity problem highlights this explanatory tradeoff between narrow explanations that are no longer justifiably drawing on racial categories and general explanations that cast too wide a net by using race concepts and draw in subpopulations than do not display the same epidemiological outcomes.

The Reification problem

[3] African Americans are fairly admixed with only modest variation in ancestry and are primarily drawn from populations originating in West and West-Central Africa, including the Yoruba in Nigeria (Zakharia et al. 2009).

The reification[4] problem with race-based studies highlights the fact that by centering *race* as a proxy for causal factors leading to the etiology of diseases, such studies neglect the explanatorily more robust role of *racism* in determination of epidemiological outcomes. Racism is increasingly seen as an exposome, which is the totality of the environmental factors, including economic, political, and social factors, to which individuals and groups are exposed. A racist exposome significantly contributes to the worse health outcomes of African Americans (and other racialized groups exposed to similar racist exposomes) (Goosby and Heidbrink 2013). In many cases of ERDs, the exposome divides populations along racial lines with far greater significance than the relatively minor between-group genetic differences.

I call this the "reification problem" because it highlights the tendency of race-based studies to *reverse* the temporal and causal relationship between race and disease risk. It is not the fact of race that constitutes the difference-making factor in many of the epidemiological cases discussed above. Rather, the social form that "race" takes, with the well-known history of racism, exploitation and discrimination, results in significant biomedical, but not genetic, differences between racialized groups (Sullivan 2013; Kaplan 2014). The case I outline below, racial disparities in birth weight, highlights the reification problem of race-based studies and argues that the approach of mechanism discovery better captures the etiology of disease phenomena.

Lorusso and Bacchini's (2015) preferred approach is race-neutral studies. This approach does not suffer from the two problems highlighted above. Race-neutral studies do not take the significant difference between racial groups that leads to a disparity in epidemiological outcomes to be population-specific genetic differences. Race-neutral studies therefore investigate any "racial" susceptibility to disease as part of the outcome of the etiological disease mechanisms rather than as

[4] Thanks to an anonymous reviewer for suggesting this term.

part of the cause (Lorusso and Bacchini 2015). Rather, they seek to represent the "general mechanism through which racism can chronically impact individual health" (Lorusso and Bacchini 2015, 61). This approach avoids the pitfalls of race-based studies by investigating the *mechanisms* that are operating to produce these disparities and paying careful attention to the dynamic role of racism as opposed to the fixed role of race. These race-neutral studies therefore fall under the category of racism-based explanations.

An illustrative case of a racism-based explanation is the disparity in cases of asthma. African American children are twice as likely as their white peers to develop asthma (Alexander and Currie 2017, 186). Previous studies had linked the higher rates of asthma in African American children to the greater incidence of low birth weights among African Americans. Alexander and Currie (2017) find that even accounting for birth weight differences, African American children still have significantly higher rates of asthma. They study children admitted to hospitals for asthma in New Jersey. They find that the racial difference in asthma rates is explained by residential segregation. Children, both white and black, in black zip codes (defined as a zip code where at least half of the children residing are African American) have higher rates of asthma than children in majority white zip codes. This is due to the fact that black zip codes are closer in proximity to sources of outdoor pollution (highways and polluting industrial plants), have homes that are on average seven years older (and higher indoor pollution due to mold and rodents), and a higher percentage of households with income less than $20,000 (Alexander and Currie 2017, 194). The reason African American children have higher rates of asthma is because they disproportionately live in black zip codes where they are exposed to these environmental factors (94 out of 676 zip codes are black in their analysis) (Alexander and Currie 2017, 195). What makes a difference to ERDs in asthma is therefore the social and historical facts of racism and residential segregation and not putative differences between races. Both white and black children in black zip codes had higher rates of asthma than their peers

of both racial groups in non-black zip codes. What makes black children more likely to have asthma than white children are the facts of residential segregation and the attendant factors discussed above (Alexander and Currie 2017).

The move to incorporate race as a proxy for a causal factor in the development of ERDs is partly driven by the downside risk of ignoring race as a relevant variable when the outcomes are clearly racialized. As we have seen, critics charge that racial categories are unwarranted as proxies for genetic diversity. This is not to suggest that race-based studies are inherently wedded to the genetic hypothesis. However, race-based studies frequently make use of race as a proxy for genetic diversity. Finding a relationship between genotypes and phenotypes, in this case SNPs that predominate in a racialized group (genotype) and disease (phenotype), remains the preeminent approach in race-based studies. These suffer from the granularity and reification problems in the context of biomedicine, on top of the challenges to genetic race concepts forwarded in the scientific and philosophical literature. Racism-based explanations avoid granularity and reification problems by following a "search for mechanisms" research process. A large share of the literature on social determinants of health and the effect of racism and low socioeconomic status on health outcomes is mechanistic (Goosby et al. 2018). As Matthews (2017) notes "… reasoning mechanistically about a phenomenon positively influences scientific hypotheses […]" (Matthews 2017, 1003). It does so because a mechanistic approach foregrounds the importance of identifying the entities and causally productive activities driving the etiology of puzzling phenomena. This approach disciplines the process of discovery by illuminating *how* the relevant causal factors fit together structurally and temporally, not just *what* those factors may be. In order to elaborate the philosophical virtues of the mechanistic approach to investigating ERDs, I first briefly describe a prominent account of the new mechanistic philosophy of science.

Discovering mechanisms

In their seminal paper "Thinking about Mechanisms," Machamer, Darden and Craver (2000) (henceforth MDC) outline a new mechanistic philosophy of science that seeks to revive and update mechanistic explanation for contemporary science and philosophy. As MDC note, "in many fields of science what is taken to be a satisfactory explanation requires providing a description of a mechanism" (2000, 1). MDC characterize mechanisms as "entities and activities organized such that they are productive of regular changes from start or set-up to finish or termination conditions" (2000, 3). Mechanisms are not "exclusively mechanical (push-pull) systems" (2000, 2) and are considered mechanisms only in so far as they are operational. Mechanisms are what biologists seek in order to explain phenomena. For instance, how plants produce their food is explained by the mechanism of photosynthesis, the phenomenon of asexual reproduction by the mechanism of mitosis, and so on.

The MDC account of mechanisms is dualistic. It includes two types of things: *entities* and *activities*. Entities (e.g., heart, cell membrane, protein) are things that, owing to their activity-enabling properties, engage in activities. Activities (e.g., pumping, transporting, binding etc.) are actions of entities that produce the changes from one stage of a mechanism to the next. Within mechanisms, entities and activities are able to produce the phenomenon due to their *organization*. MDC (2000) write, "entities often must be appropriately located, structured, and oriented, and the activities in which they engage must have a temporal order, rate, and duration" (2000, 3). Mechanisms are *regular* in so far as they operate in more or less the same way under the same conditions. Furthermore, if the description of the mechanism is complete, then there must be *productive continuity* from the start or set-up to the end or termination condition. That is, there will be no gap in our knowledge of each step in the production of the phenomenon (2000, 3).

In their 2013 book *In Search of Mechanisms: Discoveries across the Life Sciences,* Craver and Darden expand on the initial MDC account. Below, I briefly discuss their account of mechanisms, representing biological mechanisms, and characterization of phenomena. I also expand on the MDC view by incorporating difference-making into the account of activities. As I show, activities as *productive difference-makers* are what bring about the changes from one stage of a mechanism to the next.

Craver and Darden (2013) refer to the representations of biological mechanisms as *mechanism schemas* (2013, 30). These schemas can take many forms (e.g., mathematical equations or visual diagrams) and have multiple dimensions. Schemas have different degrees of completeness. If there are multiple *black boxes,* which refer to parts of mechanisms whose functional role and nature are unknown, then the schemas are more like initial sketches. There can also be *grey boxes,* which refer to parts whose functional role is known but little else (2013, 30). Depending on the amount of evidential support, mechanism schemas can be *how-possibly*, *how-plausibly*, *or how-actually* (2013, 34). As the terms suggest, how-possibly schemas "describe how a set of parts and activities might be organized such that they exhibit the explanandum phenomenon" (2013, 34). How-plausibly schemas have greater evidential support than how-possibly schemas as they appear plausible after other possible schemas have been ruled out by accumulating evidence. How-actually schemas have been well confirmed and all the parts and activities are well characterized (e.g., the mechanism of protein synthesis).

The most important step in investigation of biological mechanisms is arguably the characterization of the phenomenon. Because the mechanism is meant to explain the phenomenon, how we characterize the phenomenon "prunes the space of possible mechanisms … and loosely guides the construction of this hypothesis space…" (2013, 52). This point is summed up nicely by

the Craver and Darden (2013) phrase "the product shapes the process." Darden (et al. 2018a) apply it fruitfully to the discovery of disease mechanisms.

However, the new mechanist literature has done relatively little to expand on a core component of mechanisms, namely activities. Before moving on to the birth weight case, I briefly outline an account of activities as productive difference-makers that extends the MDC characterization of activities as "types of causes" and "producers of change." My proposed account of activities as productive difference-makers exemplifies the explanatory virtues of the mechanism discovery approach by highlighting productive continuity across stages of mechanism from start or set-up to the explanandum-phenomenon. In what follows, I briefly discuss the difference-making and its fruitful addition to the activities view.

Activities as productive difference-makers

Difference-making approaches to causal explanation have in recent years become preeminent in the analysis of causation and scientific explanation in philosophy of science, with prominent accounts forwarded by Woodward (1997; 2003; 2010), Waters (2007), Strevens (2008), and Weslake (2010). Difference-making as a philosophical notion captures both our ordinary intuitive sense of what matters in causation and accords with scientific practice. Difference-making broadly conceived characterizes the relationship between cause and effect, and explanans and explananda, as a particular kind of causal influence running from the cause/explanans to the effect/explanandum where change to the cause/explanans results in change in the occurrence of the effect/explanandum.

Woodward (1997; 2003; 2010) has advanced an influential difference-making view of causal explanation. According to Woodward, causation (and therefore explanation) is a relationship between two variables that can each have at least two values. Woodward's is a difference-making

approach because he takes the core desideratum of explanations to be answering what-if-things-had-been-different questions (w-questions). Woodward provides an account of which counterfactuals count as causal. According to Woodward, explanatorily valuable counterfactuals are made true by an exogenous causal process he calls an "intervention" (Woodward 1997, s29). Woodward defines interventions as follows:

> An intervention on X with respect to Y is an idealized experimental manipulation of X which causes a change in Y that is of such a character that any change in Y occurs only through this change in X and not in any other way (Woodward 2010, 290).

Woodward's interventions are not necessarily actual or possible human interventions. Natural phenomena, such as a floods or natural selection, may also be considered interventions. Interventions are an idealized causal activity which may or may not be satisfied in experimental sciences. Furthermore, Woodward is not providing a reductive account of causation but elucidating how certain causal relationships can be explained in terms of others. After all, intervention is itself a causal concept. However, experimental science involves the uses of known causal relationships to discover others. In other words, "in order to test some causal claims we must assume the truth of others" (Woodward 1997, s31). Woodward's difference-making provides an attractive standard for generating and evaluating explanatory claims.

For our purposes, I draw on Woodward's view to block a prominent criticism of new mechanism and the activities view forwarded by Franklin-Hall (2016). According to the critique, the mechanistic approach is explanatorily deflationary because it does not provide a standard that all activities share and that distinguishes causal productivity (within a mechanism) from irrelevant causal occurrences (such as the gravitational pull of Mars). Indeed, the early activities view explicitly eschewed providing any philosophically unifying characteristics for activities (Machamer 2004;

Bogen 2008). By incorporating difference-making into an account of activities I propose a way to block Franklin-Hall's (2016) explanatory challenge. Activities are *difference-makers*, because intervening on the variable of an activity (e.g., its rate) will alter the occurrence of the change it produces. Furthermore, I add to Woodward by noting that activities are *productive* because they bring about the next stage of a mechanism, transcription produces a messenger RNA, pumping produces the movement of blood out of the heart, phosphorylation produces an active form of an enzyme, etc. However, activities are not *mere* difference-makers. Rather, they are distinguishable from difference-makers that are merely background conditions (e.g., temperature, pressure, etc.) because they make the next stage of a mechanism *expectable* from their operation. Conceiving of activities as productive difference-makers both provides a standard by which to distinguish activities from irrelevant causal occurrences (they make a difference to the occurrence of a change) and identifies their role in mechanisms (they produce the next stage of a mechanism).

The concepts briefly discussed above are the core elements of mechanistic explanation, and they are the basis of philosophically conceptualizing, building, and evaluating explanatorily robust mechanism schemas in the life sciences. As I show below, the features of mechanistic explanation are better suited to addressing the challenges of the granularity and reification problems when proposing the etiology of epidemiological racial disparities.

Racial birth weight disparities in the United States

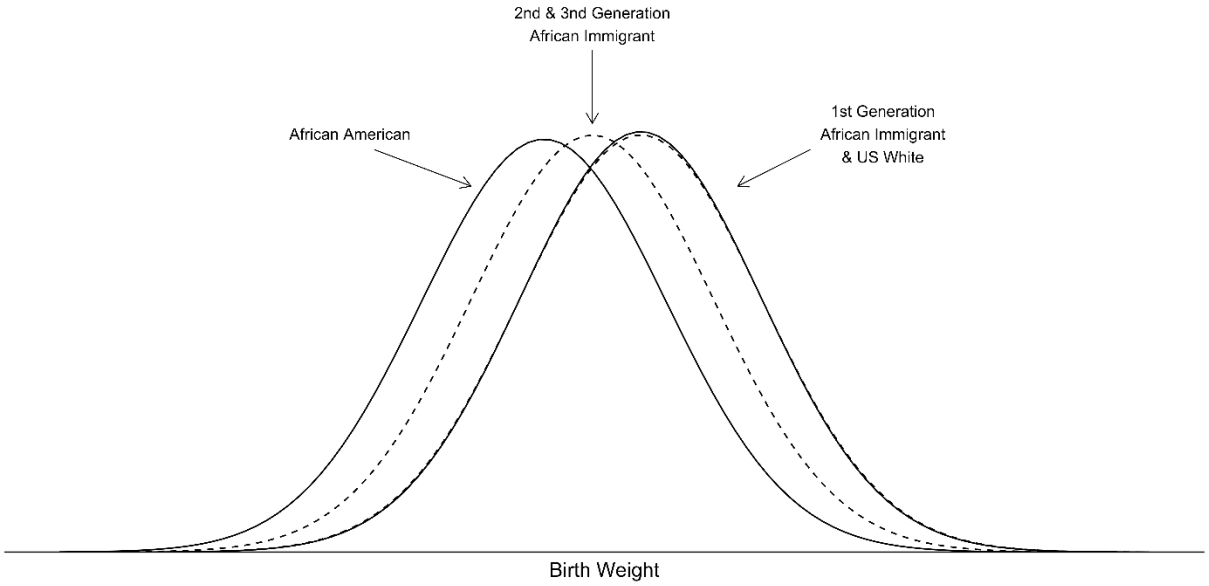

Figure 1: Schematic representing the comparative mean birth weights of US white, US black, and recent African immigrants. [Note: figure from Kuzawa and Sweet 2009, 9]

Figure 1 represents racial disparities in birth weight (races are based on self-report). African-American women are twice as likely as their white peers to have low birth weight offspring (Kuzawa and Sweet 2009; Goosby and Heidbrink 2013). But note the even more puzzling phenomenon that first generation African immigrants have birth weights comparable to US whites. In order to explain the phenomenon of racial disparities in birth weight, let us build a mechanism schema from existing research into the topic.

Multiple studies have demonstrated low birth weight among African Americans. Centers for Disease Control and Prevention data shows that African American women are twice as likely to have low birth weight births as US whites, and 2.69 times more likely to have very low birth weight births (CDC 2005; Kuzawa and Sweet 2009). This disparity has been consistent over several decades (Kramer et al. 2006; Kuzawa and Sweet 2009). The racial birth weight disparity is made all the more puzzling by the fact that recent African immigrants born overseas have birth weight distributions that are nearly identical to US whites (Forna et al. 2003). However, a study conducted in the State of

Illinois found that over subsequent generations the descendants of recent African immigrants had birth weights that were approaching the African American mean (Figure 1; Collins et al.2002; Kuzawa and Sweet 2009).

In accounting for the racial disparities in birth weight in the US, a primarily *genetic* mechanism seems highly implausible. The birth weight of first-generation African migrants is not significantly different from white American birth weights. Surprisingly, second and third generation African immigrants have birth weights whose mean begins to approach the birth weight of African Americans and after several generations there is no statistically significant difference in their mean birth weights (Kuzawa and Sweet 2009, 5). Furthermore, several studies have shown the low heritability of birth weight (Vlietinck et al.1989; Whitfield et al. 2001). The change in the African migrant birth weight figures across generations suggests that there are environmental factors within the United States that affect both groups (who are racialized as black regardless of national origin).

That environmental factor is the different *exposome* to which white and African Americans are subject. In order to adequately explain low birth weight in African Americans we must include the social level and the role of structural racial inequality. The link between racial discrimination, resulting chronic stress, and low birth weight/preterm birth is well established (Goosby and Heidbrink 2013, 636). Chronic stress also leads to low birth weight among white women. However, when the stressor, such as poverty or low income, is removed, white birth weights return to normal levels. What is surprising is that equivalent rises in income for African American women did not have a statistically significant effect on birth weight, i.e., the birth weights remained as low as before (Goosby and Heidbrink 2013, 638). It is the fact that in such cases proxies for racism--discrimination, unemployment, low socio-economic status, etc.—are not explanatory that justifies looking beyond simple racism-based explanations to the disease mechanisms of embodiment-based

explanations. Below, I discuss the evidence for embodiment of disparities in birth weight between groups racialized as black and white in the United States.

Kuzawa and Sweet (2009) argue that chronic stress experienced by African Americans creates an intrauterine environment which subtly alters fetal development, most importantly, increased maternal cortisol, insulin, and blood pressure. The difference-making entity in this process is cortisol which, upon being absorbed through the placenta by the fetus, acts to induce a slow-down in fetal growth and in high enough doses to induce pre-term birth (Kuzawa and Sweet 2009; Goosby and Heidbrink 2013).

Furthermore, there is evidence, although not conclusive for a how-actually mechanism, that some of these fetal alterations may be epigenetic. Epigenetics refers to modifications of the rate of expression of genes without any alteration to the nucleotide sequence of DNA. The most commonly studied mechanisms of epigenetic change are histone modification, which alters the proteins around which the DNA is wrapped, and DNA methylation which adds a methyl group to CpG regions of DNA, effectively silencing them (Kuzawa and Thayer 2011). Recent studies have established a relationship between certain types of exposures and epigenetic changes, including harmful environmental exposures resulting in disease-promoting epigenetic changes (Bagby et al. 2019).

Assessing the evidence

There are three crucial lines of evidence that may be brought together to propose a mechanism for low birth weight in African Americans: (i) the differential exposure of African American women to psychosocial stressors, (ii) the effect of acute stress on the metabolism and physiology of African American women, and (iii) the resulting embodiment of these cumulative stressors in African Americans. I will review the evidence for each in turn.

It is well-established that African Americans are disproportionately exposed to high degrees of social stressors (Sternthal et al. 2011). This is due in large part to racial discrimination and economic inequality (Wilson and Rodgers 2016). African American women disproportionately work in low wage jobs, are more likely to live in poverty and extreme poverty in comparison to their white counterparts and have little wealth (Wilson and Rodgers 2016). Even middle-class African Americans "are more likely to live in conditions where they are exposed to, or in close proximity, to concentrated disadvantage, high unemployment rates, pollution, violent crime, and poor housing conditions" (Goosby and Heidbrink 2013, 631-632). All of these factors contribute to the differential exposure of African American women to multiple social stressors.

The impact of stress on health is well-documented. *Psychosocial stress* is a productive difference-maker, i.e., an activity, in a number of disease mechanisms. Among the changes it produces are rapid cellular degradation (Epel et al. 2004) and elevated cortisol and blood pressure. These in turn increase the risk of developing diabetes and heart disease (McEwen and Gianaros 2010). Psychosocial stress induces excess production of the stress hormone cortisol. And there is evidence that cortisol produced due to antenatal stress is transferred through the placenta into the fetal bloodstream (Zijlmans et al. 2015; O'Donnell and Meaney 2017). Cortisol is a hormone that regulates the hypothalamic-pituitary-adrenal axis (HPA) (responsible for maintaining homeostasis) response to stress along with the maintenance of pregnancy and the onset of birth (Stewart et al. 2015). Cortisol and corticotropin-releasing hormone (CRH) rise under normal conditions during the course of a pregnancy. However, excess maternal CRH increases the risk of premature and/or low birth weight births (Phillips et al. 1998; Goosby and Heidbrink 2013) by producing poorly vascularized placentas and thereby restricting intrauterine growth (Stewart et al. 2015).

Finally, there is the transgenerational aspect of low birth weight in African Americans. This is the part of the mechanism for which there is the least evidence, and which is drawing attention in research. There are two factors that may contribute to the fact that low birth weight births are transgenerational: first, the perpetuation of the environmental factors (e.g., psychosocial stressors) which lead to low birth weight offspring and second, epigenetic modifications that increase the risk of low birth weight offspring having offspring of their own with the same low birth weight phenotype even in the absence of the initial causally productive exposome. Evidence for the first factor is discussed above. As for the second, there is evidence fetal programming is responsible for perpetuating low birth weight outcomes even in the absence of the original inducing environment, although the evidence is limited and the exact mechanism for this is not currently known (Drake and Walker 2004; St-Pierre et al. 2012; Scholaske et al. 2018). McDade (et al. 2019) find evidence for a relationship between low socioeconomic status (SES) and epigenetic changes in a number of CpG sites across a large portion of the genome. DNA methylation was over-represented in sites associated with skeletal development, immune function, and development of the nervous system (McDade et al. 2019). Further research is needed to find out what mechanisms, if any, are mediating these effects.

Building the mechanism schema

We now have a how-plausibly mechanism for low birth weight among African Americans (Figure 2) (productive difference-maker activities in italics). Acute stress due to racial discrimination and structural inequality *induces* a change in the metabolism and physiology of African American women. This creates an intrauterine environment with *increasing* cortisol, insulin, and blood pressure (BP). Intrauterine and fetal metabolism of maternal cortisol *restricts* fetal growth. Ongoing stress

reinforces the mechanism[5]. Even if the maternal exposome were to have reduced stress, fetal programming potentially makes low birth weight birth transgenerational, although more research is needed on this front (Scholaske et al. 2018).

This low birth weight mechanism is an illustrative case of embodiment-based explanations. As we have seen, although West Africans, black Caribbeans and African Americans share genetic ancestry, these three subpopulations do not share similar health outcomes when compared to white Americans. Race (as a proxy for some genetic variable) therefore does not *productively make a difference* to the occurrence of the low birth weight disparity. Rather, by allowing the phenomenon to guide us we see that genetic race concepts are inadequate. The *exposome* to which African Americans are subject productively makes a difference to racial birth weight disparities. There may be a transgenerational component which, in the terminology of Kuzawa and Sweet (2009), means that race *becomes* biologically "embodied" with respect to ERDs. Rather than meaningful biological differences leading to racial classification, the social process of racial categorization ends up producing meaningful biological differences. In other words, racism acts as a start-up condition of a biological mechanism that produces meaningful biological differences between socially defined races.

What makes mechanism discovery a promising approach for the explanation of and intervention on epidemiological racial disparities is that it provides productive continuity between proposed causal factors (racism, genetics, embodiment) and disease incidence by showing how the different parts of the mechanism, entities and activities, interact to produce the phenomena. As we see with the birth weight case, mechanism discovery avoids the granularity and reification problems. By identifying the exposome as the productive difference-maker, either in producing the disease or

[5] See discussion of evidence for details.

interacting with genetic factors to mediate disease risk, there is no need to lump or split different subpopulations racialized as black in the United States in order to articulate genetically similar populations. In the low birth weight case, it shows the correct direction of the production of the low birth weight phenomenon from the social fact of racism to the biomedical racial disparities. Furthermore, mechanism discovery does not detract from, but rather enhances, our ability to propose interventions to arrest and reverse these disparities by, for instance, identifying the role of productive difference-makers such as a racist exposome and fetal programming.

Conclusion

Mechanism discovery is a philosophically well-developed and fruitful approach to investigate how epidemiological racial disparities are created and maintained. The prevailing reliance on discovering statistical association between putative causal factors, genetics in particular, and disease risk has serious explanatory limitations. Using race as a proxy for genetic diversity opens up race-based studies to the granularity and reification problems. By expanding the new mechanist concept of activities to a view of activities as productive difference-makers, the mechanism discovery approach I propose addresses a prominent critique of the new mechanism approach and shows the explanatory virtues of applying mechanism discovery to epidemiological racial disparities. Constructing biomedical mechanism schemas that incorporate and highlight the role of productive difference-makers enables the identification of all and only the actual difference-makers to disease incidence. The kinds of mechanisms that produce racial disparities may have genetic, biological, and/or social productive difference-makers, making mechanism discovery a potentially interdisciplinary effort in charting the mechanism schemas of racial epidemiological difference. Furthermore, mechanism discovery could be useful in designing policy and medical interventions to address racial disparities in health (Efstathiou 2012; Hardimon 2013), among other spheres, as the

philosophy of mechanisms is increasingly being used in medicine (Russo and Williamson 2007; Darden et al. 2018b; Kennedy and Malanowski 2019).

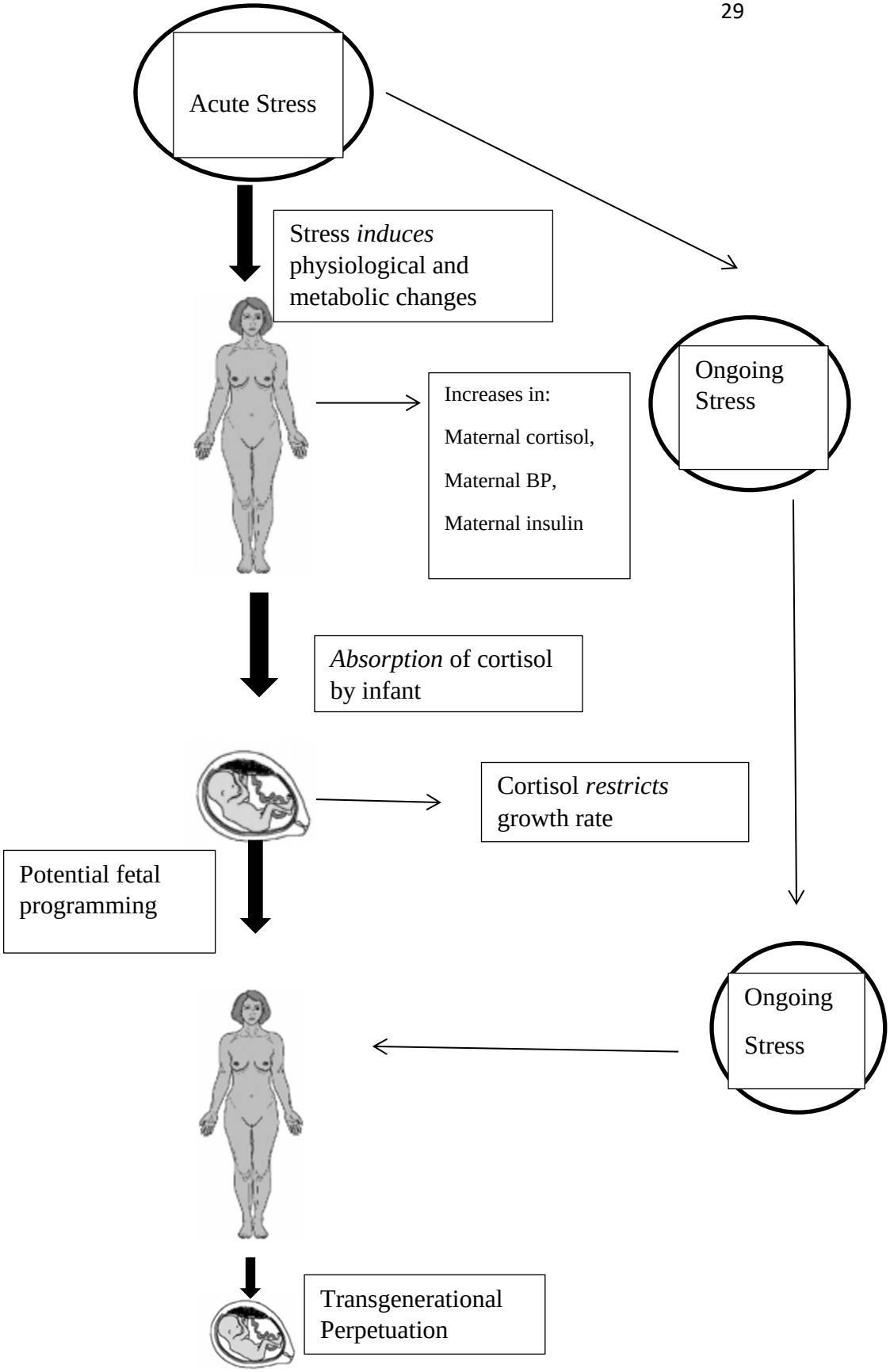

Figure 2: Diagram of the mechanism schema for low birth weight births in African American women, details of which are discussed above. [Note: adapted with modifications from a pathways model appearing in Goosby and Heidbrink 2013]

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