Evolutionary mismatch: project 2

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Draft date: June 13, 2019
Word count: 8858.

Morris Dissertation manuscript No.
(will be inserted by the editor)

Be fruitful and multiply

Fitness and health in evolutionary mismatch and clinical research

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Received: date / Accepted: date

Abstract Evolutionary mismatch is, roughly, poor fit between an organism and its environment. Researchers in evolutionary medicine have proposed mismatch as a possible cause for morbidity and mortality in contemporary *Homo sapiens* populations. Mismatch hypotheses are often taken to provide an evolutionary explanation for the health outcome in question, while simultaneously offering possible interventions for researchers and clinicians to pursue. A problem: fitness outcomes and health outcomes are distinct. Natural selection operates on fitness, not on health per se. There are cases where increased health may not contribute to fitness in the modern environment. I propose an approach for using evolutionary mismatch in clinical research which sidesteps this problem. The gist of the proposal: given structural analogies between environmental causes of morbidity and environmental causes of fitness reductions, evolutionary mismatch can be used as a heuristic to shrink the space through which clinical and public health researchers must search for possible interventions in response to contemporary health problems.

Keywords Evolutionary mismatch · Fitness · Evolution · Health · Research · Heuristics

1 Introduction

This paper concerns the use of evolutionary mismatch hypotheses in evolutionary medicine. Evolutionary mismatch is a putative biological phenomenon which results when an organism (or population, or trait) which evolved in one environment experiences an environmental change with health or fitness consequences. I argue that the mismatch framework can be used as a heuristic for discovering interventions, even when it is not used for true ultimate explanations.

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Evolutionary medicine as a discipline has attempted to apply the insights of evolutionary biology to clinical research and practice. The general motivation for evolutionary medicine is simply this: humans are evolved organisms, and understanding how and why we evolved the way we have may shed light on our physiological, social, and psychological needs. Evolutionary biology, in this framework, helps us to understand not only why we have the needs we have, but may also help us develop ways to meet those needs. If nothing else, evolutionary explanations must be the ultimate explanations for many causes of human morbidity and mortality. Consequently, Nesse and Williams (1994) tell us, "Nothing in medicine makes sense, except in the light of evolution."

Mismatch hypotheses have been used implicitly and explicitly throughout evolutionary medicine and evolutionary psychology, and as a result putative mismatch phenomena include allergies, anxiety, atherosclerosis, autoimmunity, breast cancer, depression, type II diabetes, obesity, and many others. (See e.g. Williams and Nesse (1991); Nesse and Williams (1994); Trevathan (1999); Gluckman and Hanson (2006); Trevathan et al. (2008); Gluckman et al. (2009); Lindeberg (2010).)

Fitness and health are different phenomena, however. I show that some putative mismatch hypotheses do not seem to involve reduced fitness, but only reduced health. Consequently, it is not clear whether mismatch is an appropriate lens for thinking about health problems.

Rather than treat mismatch as a proper explanation, then, I propose treating mismatch as a heuristic—a framework for identifying hypotheses and targets for clinical or public health intervention, rather than an explanation in its own right. If mismatch thinking is fruitful in a clinical context, then treating mismatch as a heuristic allows the researcher to sidestep the problem I raise.

This paper does not present a comprehensive case for adopting a mismatch heuristic. Instead, seeing that mismatch thinking is already in use in evolutionary medicine, I warn mismatch researchers of a problem in the project and show how they can escape the problem.

2 Fitness and health

2.1 Evolutionary medicine

Evolutionary medicine is a discipline which seeks to apply the insights of evolutionary biology to clinical research and practice. It dates to at least 1991, with the publication of Williams and Nesse (1991). (Earlier work, e.g. Eaton and Konner (1985), employs similar reasoning and reflects on similar themes.) Given that *Homo sapiens* is an evolved species, our physiology and psychology are also evolved. At a bare minimum, then, ultimate explanations for our physiology and psychology will be evolutionary in nature (not necessarily to say that the explanations will be adaptationist). Perhaps, the thinking goes, understanding our evolutionary history and the nature of evolutionary phenomena can help us better understand our own physiological or psychological needs.

Nesse and Williams (1994) point to six general evolutionary explanations of vulnerability to disease: (1) defenses (unpleasant defense responses to illness, e.g. a cough when one has pneumonia), (2) infection (forces which cause humans to

develop immune responses which in turn drive pathogen evolution), (3) novel environments (new environments to which a species is not well-adapted), (4) genes (novel deleterious effects from ancient, benign genes in new environments, as well as heterozygote-advantage genetic disorders), (5) design compromises (evolutionary trade-offs), and (6) effects of past evolution (e.g. the fact that in humans food must pass by the trachea).

Evolutionary medicine has been criticized for a general adaptationism and for seeming failures to provide clinically-relevant hypotheses. (Valles (2012); Cournoyea (2013)) I am generally quite sympathetic to these critiques. However, the key insight of evolutionary medicine—that our evolutionary history explains, at the very least, our current physiological and psychological needs—seems worth preserving. In particular, I am interested in so-called mismatch hypotheses: hypotheses inspired by the view that humans are in some ways better-adapted to life as hunter-gatherers on the African savanna than to life in post-agricultural societies.[1] This idea is captured primarily in (3) above: for much of *Homo sapiens*, life no longer resembles a primary environment in which we evolved—and this has had impacts on our health. Key to this approach is the view that humans are still very similar to our ancestors on the savanna, such that our physiological and psychological needs (broadly-construed) will also be very similar. This is not a claim that humans are frozen in evolutionary time, of course, but rather that the quantity and significance of evolutionary changes are relatively small.

2.2 Evolutionary mismatch

Before we dive into the mismatch concept itself, one more concept should be sketched: the *Environment of Evolutionary Adaptedness*, or EEA. This term refers, roughly, to the environment for which a lineage has evolved—its ancestral environment.[2] The EEA is a tricky concept to characterize with precision, and of necessity the following discussion makes some idealizing assumptions and elisions.

Here is an intuitive way to think about the EEA: populations are made up of organisms with varying capabilities and vulnerabilities, which enable them to leverage certain environmental features for their own use but which leave them vulnerable to other detrimental environmental features. Given enough time in a particular environment and some stability in the environment's selection pressures, the population's distribution of capabilities and vulnerabilities will likely change such that it comes to 'fit' that environment better than it had in the past. In

[1] Much evolutionary medicine and mismatch-oriented work (e.g. Eaton and Konner (1985), Nesse and Williams (1994), Gluckman and Hanson (2006), and Lindeberg (2010)) are interested in major environmental changes experienced by the human species, and point to the transition from foraging to agriculture—with its alterations in diet, social structure, activity levels, and so forth—as a particularly significant change.

[2] For the sake of brevity and in order to maintain some terminological continuity, I retain the 'EEA' terminology, which I take to be roughly synonymous with how others use terms like 'ancestral environment'. I do not use 'EEA' to signal any particular theoretical commitments. Some characterizations of the EEA, e.g. the original characterization given in Bowlby (1982), focus on adaptations which enable the population to thrive in the EEA. I encourage the reader not to hunt too enthusiastically for how each trait I mention is an adaptation to a particular adaptive problem: I *do not* make that claim, and my use of 'EEA' should not be construed to imply it.

such a case, the set of traits undergoing major directional change will presumably get smaller.Environments are rarely perfectly stable, but sometimes a significant change will occur which exposes new vulnerabilities or blunts the efficacy of old capabilities such that one can see a meaningful discontinuity between the environments. In such a case, the previous environment would be the (or perhaps an) EEA.The EEA, then, is a historical environment for a population (or its lineage), the selection pressures of which it has adapted to solve. Importantly, as I use the term, relevant features of the EEA may be the absence of features present in the novel environment: a certain type of predator, for example. That an organism lacks the capability to cope with a particular novel predator will often be due to the fact that the organism's lineage did not need to cope with the predator. In this case, we see no particular adaptations failing; instead, we see a vulnerability laid bare by the changed environment.

I take it that none of this is novel to the reader, but I review it to situate the EEA concept: it is, roughly, that environment to which the species is primarily adapted. If a deer population has evolved in an environment with no predators, then its EEA is a predator-free environment—and the introduction of predators would be *evolutionarily novel*. In other words, populations may have traits to deal with particular adaptive problems, but not others. Most mammals, for example, have a terrestrial, rather than marine, EEA. For the most part, in other words, *Mammalia* has not evolved to solve the adaptive problems of the ocean.

Evolutionary mismatch is often taken to involve a negative effect on an organism (or population) due to an environmental change relative to its EEA. (Lloyd et al. (2011); Sih et al. (2010)) The mismatch concept itself has undergone relatively little focused philosophical examination (except for Lloyd et al. (2011), Garson (2015), Cofnas (2016), and Morris (2018)) and, consequently, there is no firm consensus on how best to understand it (a bit more on this later). I will bracket that debate here, as the clinical use of mismatch which I propose here does not rest on a particular characterization but rather on the general themes echoed in most mismatch hypotheses.

Mismatch, then, involves an environmental change which negatively affects a population or its member organisms. The population adapted to one environment, the EEA, and is now in a different environment. In evolutionary medicine, the mismatch concept is employed to explain the prevalence of much morbidity and mortality in contemporary *Homo sapiens* populations. Our EEA, the thinking goes, is the African savanna—particularly, hunting and gathering on the savanna—and to the extent that our current environment differs from our EEA in a way which affects us negatively, there is an evolutionary mismatch. To explain a bit more clearly, I will give three cases of putative mismatch: scurvy, myopia, and reproductive cancers. In the interest of brevity, I will background some of the evolutionary storytelling with respect to the origins of the traits or their status as adaptations, neutral traits, etc. Instead, I will focus primarily on the negative effects of the new environment relative to the EEA—the mismatchy part.

Ascorbic acid (vitamin C) is an essential nutrient for humans which plays a role in various physiological functions, including wound healing and the immune system. *Homo sapiens* is part of the haplorhine (dry-nosed primate) lineage, along with the other apes, the monkeys, and the tarsiers. Approximately 50 mya, the haplorhine lineage split from the strepsirrhine (wet-nosed primate) lineage, which includes the lemurs, bush babies, pottos, and lorises. The strepsirrhines, like the

vast majority of mammals, are capable of synthesizing ascorbic acid and do not require it in the diet. The haplorhines, on the other hand, are not capable of synthesizing ascorbic acid and must obtain it from their diet. Given ascorbic acid's critical role in bodily function, it might seem odd to lose the ability to synthesize it—and yet our lineage has. Presumably, the thinking goes, primitive haplorhines were at least partially frugivorous and did not require the ability to synthesize a nutrient which was already abundant in the dietary environment. As a result, the ascorbic acid-synthesizing trait was lost in the haplorhine lineage. (Pollock and Mullin (1987)) The human EEA, then, is an environment with abundant dietary vitamin C. If our environment changes such that we can no longer obtain vitamin C through the diet—say, due to the fact that we are on a long ocean voyage without fruits and vegetables—we can develop scurvy, a potentially life-threatening illness. In such a case, there is (allegedly) an evolutionary mismatch. This mismatch can be alleviated by recreating a feature of the EEA: ready access to fruits and vegetables.

Myopia, or near-sightedness, is another putative example of mismatch. Lindeberg (2010) (133,142-144,147-148) argues that insulin resistance may play a causal role in the etiology of myopia.[3] Contemporary human diets seem to increase insulin resistance relative to the traditional diets of hunter-gatherers. In particular, it seems that chronically high blood glucose levels appear to increase the insulin resistance of tissues, which causes the pancreas to increase insulin levels in an attempt to "overcome the resistance" (in Lindeberg's words) in the cells. To simplify a bit, high serum insulin levels appear to result in higher levels of free insulin-like growth factor-1 (IGF-1). High IGF-1 levels in turn downregulate the activity of retinoid receptors in the cell—receptors which inhibit cellular growth. Retinoids produced in the retina and sclera help to inhibit growth of the eye. If retinoid receptors are down-regulated by excessive IGF-1, the eye may continue growing beyond what is useful for adequate vision, resulting in an eye which focuses light in front of the retina, rather than on the retina—resulting in blurry distance vision. If all this is right (and at this point it is hypothetical), then increased frequency of myopia in contemporary populations relative to myopia frequency in hunter-gatherers may be explained by the evolutionarily novel consumption of insulin resistance-promoting food in the diet. In other words, consuming high levels of food which promote insulin resistance is a change relative to the human EEA, and has a corresponding health effect. To reduce myopia (and similar problems caused by evolutionarily novel foods), Lindeberg (2010) suggests the consumption of foods similar to those of humans' hunter-gatherer ancestors—foods which do not promote insulin resistance.[4] To be clear: this hypothesis is not yet well-tested. Whether the hypothesis is correct or incorrect is beyond my purposes here, which is simply to clarify the sorts of mismatch hypotheses advanced in evolutionary medicine.

Finally, we turn to reproductive cancers in women; specifically, to breast cancer. In contemporary populations, most women bear fewer children, have children

[3]Nesse and Williams (1994); Gluckman and Hanson (2006); Gluckman et al. (2009) all advance mismatch hypotheses of myopia as well, though their proposed mechanisms of action differ.

[4]Other discussions of so-called 'ancestral' or 'Paleolithic' diets include Shatin (1964), Shatin (1967), Eaton and Konner (1985), Eaton et al. (1999), Lindeberg et al. (1997), Lindeberg et al. (2001), Lindeberg et al. (2007).

later, and spend less time breastfeeding relative to women in hunter-gatherer populations. As a consequence, it seems very likely that contemporary women experience a higher quantity of menstrual cycles than forager women do, and that they spend more time in the interval between menarche and first full-term pregnancy. Each menstrual cycle involves cellular turnover in the reproductive organs, and the time from menarche to first birth is a time of particularly elevated turnover in the breast duct glandular and epithelial cells, thereby increasing the risk of potentially malignant mutations. Given that breast cancer appears to occur at significantly lower rates in hunter-gatherer societies than in contemporary societies, it seems plausible that some feature of the environment is responsible for the difference. Evolutionary medicine researchers have proposed that changing reproductive patterns constitute part of that explanation. (Nesse and Williams (1994): 179-181, Eaton and Eaton III (1999): 430-436) Note here, again, that features of the EEA (short interval between menarche and first birth, lifetime menstrual cycles estimated at potentially fewer than 100, per Sievert (2008): 185) have changed in contemporary societies, and there has been a commensurate increase in breast cancer frequency. Eaton and Eaton III (1999) suggest that even in the absence of a change in reproductive decisions, it may be possible to recreate the ancestral hormonal milieu in part by using certain oral contraceptives to reduce menstrual cycles. (Sievert (2008) argues that the evidence does not support such an intervention.)

Again, I stress the hypothetical nature of the claims I describe here. I describe them here only to give the reader a picture of the kind of mismatch hypotheses that are proposed in evolutionary medicine. They strike me as interesting, plausible, and potentially fruitful—well worth investigating, in other words. To review briefly: in a mismatch hypothesis about health, a human health outcome is taken to be caused by an environmental change relative to the EEA, such that the human is less-well-adapted to the new environmental character(s).[5] The EEA is then examined for possible interventions, such that the particular features of the EEA can be implemented in the contemporary environment—or, at least, adequately simulated as in the contraceptive proposal above.

2.3 The trouble with fitness and health

In this section, I show that the concepts of fitness and health come apart, and show that this is a problem for mismatch hypotheses in evolutionary medicine.

At this point, it is worth getting a bit more clear on the notion of evolutionary fitness. The view I develop here does not depend on any specific characterization of fitness, but for the sake of convenience I will draw briefly on the propensity interpretation of fitness advanced by Mills and Beatty (1979): an organism's fitness is its propensity to leave offspring in the next generation in a particular environment. Consider (from Darwin (1859)) a population of deer in an environment with wolf predation: a variant which is fleeter of foot will generally be more likely to survive and reproduce than slower variants in the population. On the Mills and Beatty (1979) view, then, the faster deer has a higher propensity to reproduce in

[5]This is not to take the position that all mismatch-relevant traits are adaptations, only that some traits—including adaptive, neutral, and deleterious traits—may perform worse in a novel environment relative to the EEA.

an environment with wolves—and, therefore, a higher fitness. In such an environment, then, there is selection pressure in favor of higher speed in deer. Were the deer exposed to no predation risk, faster deer might have no fitness advantage at all.

Note above, however, that none of the three mismatch hypotheses I describe actually involve a claim about decreased fitness as a result of environmental change. Instead, the claims are about health outcomes: scurvy, nearsightedness, and breast cancer. Indeed, Lindeberg (2010) (148) implicitly acknowledges that in the contemporary environment, glasses reduce selection pressure against susceptibility to myopia. In other words, the mere presence of myopia may not be fitness-reducing in an environment where vision correction is available. Presumably, however, there is some meaningful sense in which myopia involves decreased health. Similarly, in the case of breast cancer which occurs late in life, potentially long after the conclusion of a particular woman's reproductive career, it is plausible that despite the devastating health consequences, the fitness consequences may be minimal—even assuming we are concerned with inclusive fitness. Further, we can consider cases where fitness and health vary differently. Take a 30-year-old, childless woman who has had a tubal ligation (and is an only child of only children). Her inclusive fitness—that is, her propensity to leave her genes in the next generation—is presumably near zero. Yet over the years, her health can improve or degrade with no variation whatsoever in her fitness.

The problem may still seem obscure: surely healthier organisms are fitter organisms, and so any environment which reduces the health of the organisms in it will also be an environment to which we can say that they are less-well-adapted than they would be to a different, health-promoting environment. This response is a fair one, and I will draw on the fitness relevance of physiological and psychological outcomes later when I propose the mismatch heuristic. For now, however, it suffices to be clear that health and fitness can come apart.

None of this is to say that health and fitness never interact, of course. Developing scurvy at the age of 20 and dying would surely be fitness-reducing and also health-reducing. The point, rather, is that evolutionary mismatch, understood as something like poor fit or poor adaptation to environment, is presumably something about fitness—the 'target' of natural selection. An organism's being less healthy due to an environmental change is not clearly *evolutionary*, if there is no fitness impact of the change. The evolutionary history part of the hypothesis—the EEA, and adaptation to the EEA but not the contemporary environment—is taken to form a rather large part of the explanation for why there is a loss of health in the current environment at all. Mismatch hypotheses are intended to help formulate interventions—e.g., by consuming an 'ancestral' diet to reduce insulin resistance. Justifying the intervention often involves appealing to the presence of certain environmental factors in our EEA. If mismatch researchers need to determine the presence (or absence) of a fitness effect before the use of mismatch is licensed in clinical research and practice, this will require a great deal of antecedent biological work which may slow rather than hasten the identification of clinically-useful hypotheses. In that case, the concept seems unlikely to be of much clinical utility except, perhaps, in more extreme cases in which, like scurvy, the fitness effect is immediately apparent.

One might worry initially that the picture I paint is unfairly bleak: sure, myopia's fitness effects may be unclear, but scurvy seems straightforward enough.

Perhaps, the interlocutor might suggest, there are many mismatch cases which bear more resemblance to scurvy than myopia. This is entirely possible. To the extent that mismatch effects are similar to scurvy—major health *and* fitness effects—the problem is less profound. Given the actual problems discussed in the mismatch literature, however, which include many of the so-called 'diseases of civilization'—diseases which often occur after the close of the reproductive career[6]—many putative mismatch cases will not be cases of reduced fitness. This is, therefore, still a problematic outcome for the mismatch theorist who thinks of mismatch as involving some sort of decreased fit to environment.

Not all mismatch theorists treat mismatch solely as a fitness phenomenon. Lloyd et al. (2011) propose a disjunctive view on which mismatch involves reduced health or reduced fitness due to environmental change relative to the EEA. On this view, if health declines in a novel environment, they can diagnose it as a mismatch—and that seems to get the mismatch theorist what she wants. The problem, though, is the opacity of the connection between the two different types of mismatch. Granted, the structure of the explanations is similar: both involve an evolutionarily novel environment having some sort of negative effect. In this account, however, mismatch is disunified as a concept. Some health mismatches will not be fitness mismatches and vice versa. This seems to drop the evolutionary core out of the mismatch explanation. An intuitive characterization of mismatch attributes that mismatch to the organism's lack of adaptation to the novel environment. If the novel environment is having a health effect but no fitness effect, however, a story about adaptation is the wrong kind of story. Moreover, specifying two different types of mismatch with no intrinsic connection does not seem to be the way that mismatch theorists think of evolutionary mismatch.[7] I say a bit more about this in section 3 when I discuss the extension of the optimal-environments account of evolutionary mismatch developed in Morris (2018) to health.

A different non-fitness-focused view of mismatch is the teleofunctional account developed in Cofnas (2016): mismatch obtains for an organism when an environment is different from the organism's EEA such that one or more of the organism's adaptive traits fail to perform their proper functions. Note that this view requires neither a fitness effect nor a health effect. As Cofnas says, this lack of concern for specific consequences means that some cases of mismatch will actually be beneficial for an organism: a mouse living in a cat-free environment may perform no predation-avoidance behaviors, but this environment is surely beneficial on this count. The challenge of using the teleofunctional account to talk about evolutionary mismatch in health is apparent: evolutionary medicine is interested in mismatch *because* researchers see mismatch as something worth alleviating. It may be possible to massage the teleofunctional account in order to employ it in evolutionary medicine, but at a first glance it does not seem to line up neatly with the clinical and public health goals of mismatch theorists.

[6] A point of clarification here: physiological or psychological changes which manifest after the close of the reproductive career can, of course, still effect fitness by, e.g., depriving descendants of 'grandparent care'. It seems plausible, however, that at least in some cases there will be no commensurate fitness effect for some disease states which occur late in life.

[7] Some, e.g. Gluckman and Hanson (2006); Gluckman et al. (2009), have proposed recognizing both evolutionary mismatch and developmental mismatch as different mismatch phenomena. This is not the same distinction I describe here.

Intermission

Let us consider what we have seen so far. We began by examining the concept of evolutionary mismatch, with a special focus on its use in evolutionary medicine. Mismatch hypotheses use some sense of poor fit to an environment (usually relative to a historical environment) to explain some phenomenon. In evolutionary medicine, mismatch is used to explain negative health outcomes like scurvy, myopia, and breast cancer.

Although there is an intuitive connection between the idea of mismatch and the observation of 'new' environmental factors like insulin resistance-promoting diets, the connection becomes a little less clear when we attempt to drill down on exactly how the evolutionary story plays an explanatory role. I have argued that some mismatch hypotheses purport to explain diseases which plausibly do not reduce fitness. In other words, this sort of "mismatch" does not look very much like a picture of mismatch focused on fit to environment. Consequently, it seems likely that mismatch hypotheses *in principle* will explain far less than mismatch researchers want them to.

In the next sections, we will examine some ways that mismatch researchers might try to handle this problem.

3 Health mismatches

Levins (1968) (14) describes phenotypes as having 'optimal' environments with respect to a particular environmental character, e.g. temperature. The optimal environment, for Levins, is the environment where the phenotype's fitness is highest. Morris (2018) develops an optimal-environments account of evolutionary mismatch: mismatch obtains for any organism which is not in its optimal environment, which is just that environment where its fitness is maximized.

Earlier, I gave some reasons to think that a fitness-centric approach is unlikely to allow for mismatch thinking of the sort that evolutionary medicine researchers do. Perhaps they should adopt an optimal-environments account of 'health mismatch', such that mismatch obtains for an organism if it is in an environment which is not its 'health-optimal' environment—that environment where its health is maximized.

The view has some intuitive appeal. If the optimal-environments account is the right way to think about evolutionary mismatch, then here we have a nice conceptual analogy: fitness mismatch involves reduced fitness relative to fitness in the optimal environment; health mismatch involves reduced health relative to health in the optimal environment. Both accounts direct our attention to considering what sort of environment would be optimal for a given organism. The accounts would simply use different concepts of optimality: one would require comparison of the present environment to an environment in which fitness is maximized; the other would require comparison to an environment in which health is maximized. Evolutionary mismatch hypotheses are always concerned with the effects of environmental change—particularly novel environmental change—and this approach would reflect that concern.

Despite these merits, however, this solution to the fitness-health problem has some substantial deficiencies which lead me to rule it out.

First, this sense of mismatch seems only vaguely evolutionary. The approach runs into the same problem as the disjunctive view of mismatch proposed by Lloyd et al. (2011), discussed above: the causal connection between health-mismatch and fitness-mismatch is dubious. They appear quite plausibly to be distinct concepts with neither leading obviously to the other or being subsumed by the other.

Second, it is harder to see how to think about health as being optimal (or sub-optimal). The optimal-environments account of fitness relies on a quantitative notion of fitness: if the organism is in an environment where its fitness measurement is not as high as it could be in a different environment, then mismatch obtains for the organism. Fitness concepts generally lend themselves to measurement of an organism or variant's total fitness, at least in principle. Health does not seem to do so. What might it even *mean* to think of health *simpliciter* as a quantitative concept? The most obvious quantifiable option—longevity—does not seem to capture the qualitative aspects which so concern us in clinical practice. Myopia may well decrease quality of life, but it may well not decrease quantity of life.

In short, then, the health-mismatch concept (1) seems to detach itself from the evolutionary foundation of the fitness mismatch concept, and (2) is less clearly coherent than the fitness-mismatch concept.

4 Excluding non-fitness hypotheses

Another approach we might take is simply eliminativist: if fitness is not impacted, then mismatch does not obtain for the organism in question. Thus, the utility of all mismatch hypotheses about health depends entirely on whether a fitness effect occurs. On this view, researchers must first identify the fitness effects of particular environmental factors, and only then proceed on to considering their health consequences.

There is a clear advantage to this view: it is immediately clear that any mismatch hypotheses about health outcomes are, in fact, *evolutionary* hypotheses. If mismatch hypotheses purport to provide evolutionary explanations, one might reasonably expect them to describe fitness outcomes—even if they also describe health outcomes.

A major worry militates against this approach. I suspect that as a methodological matter fitness outcomes will only be known after health outcomes are already understood. If this is the case, then mismatch hypotheses might provide a deeper understanding of health outcomes, but they are unlikely to facilitate the development of new, effective clinical interventions—surely a major desideratum for evolutionary medicine research.

A critic might respond that the process of investigating the fitness effects of a particular health outcome may reveal proximate causes which lead to new interventions. This cannot save the eliminativist approach, however: the eliminativist's proposal (as I have stipulated here) is that mismatch explanations only apply in cases where fitness effects are known to be deleterious. We explore mismatch hypotheses because they suggest explanations and interventions which are of clinical interest. It seems that in order to investigate the fitness effects of an environmental change which caused a deleterious health outcome, we would need to accomplish the following: identify the environmental change which appears to have caused the change; identify a health effect of interest in the novel environment; identify

fitness in the past and novel environments. This seems to carry the investigation a step further than is necesssary for thinking about the particular health outcome in question.[8] This does, however, suggest another approach: the use of mismatch as a clinical heuristic for hypothesis formation.

5 Mismatch as clinical heuristic

Thus far, we have seen a problem for the use of evolutionary mismatch in health research. We have further seen that two superficially-plausible solutions fail. In this section, I propose my solution to the problem.

I begin by discussing the notion of heuristics coming out of early artificial intelligence research (e.g. Simon and Newell (1971)), and describe some of the features of heuristics as characterized by Wimsatt (2006, 2007). Following e.g. Nesse (2008), I argue that evolutionary mismatch has value as a heuristic; I further suggest that this employment can sidestep the fitness-health tension in mismatch research which I have laid out in the earlier parts of this paper.

The basic view can be summarized as follows: when I suggest using the mismatch framework *as a heuristic*, I mean that we can use the framework to shrink the search space when looking for possible solutions to clinical problems. The *nature* of the mismatch heuristic is a form of analogical reasoning. Further, my argument is focused primarily on the merits of mismatch *as a heuristic* rather than *as an explanation in its own right*—not on the merits of the mismatch heuristic relative to other heuristics in the health sciences.

5.1 Heuristics for discovery

Early artificial intelligence (AI) researchers recognized a challenge in trying to develop problem-solving machines: computers run on algorithms, i.e., unambiguous sets of instructions which will take one unfailingly from input to consistent output. One approach to problem-solving is to map out a problem space, or search space, within which the program can search for solutions to the problem. Naturally, the limits of computational power constrain the extent of the possible search. A sufficiently-large problem space will render an exhaustive search computationally intractable, and triage is required.

The rules of thumb for shrinking the problem space are heuristics. Heuristics help us identify those parts of the problem space likely—or unlikely—to be profitable, should we decide to search them (Simon and Newell (1971)). It is important to be clear: heuristics are imperfect rules. Even very fruitful heuristics will sometimes exclude correct solutions. The value of a heuristic, then, is not that it serves unerringly as our North Star but, rather, that following the heuristic will tend to lead us to the right answer—or at the very least, rule out many wrong answers.

Wimsatt (2007) (76-77) describes four general features of heuristics in the sciences: (1) heuristics sometimes generate false outputs; (2) heuristics are cost-effective; (3) the false outputs of heuristics will be nonrandom; (4) heuristics trans-

[8] This does not, of course, mean that there is no reason to investigate fitness outcomes. The point is just that identifying the environmental cause of a health outcome is all we need *for clinical research*.

form the problem into a "nonequivalent but intuitively related problem." I will touch on each of these briefly, and then consider the latter two in section 5.3 below. To (1): as Wimsatt says, heuristics are not truth-preserving algorithms. Even when applied correctly, rules of thumb sometimes lead us astray. In other words, sometimes the correct solution is hiding in a different part of the problem space which our heuristic told us not to search. One can think here of how a particular decision in chess might generally be unwise (e.g. sacrificing a queen to capture a pawn), but could contribute to victory in a specific game. I take it that I have already explained (2) sufficiently above. To (3): the idea here is that due to the structure of a particular heuristic, it will generate wrong answers in response to certain variations of a more general problem. Newtonian physics might be a useful heuristic when one is attempting to calculate the trajectory of a bullet fired from a human-portable firearm, but will reliably lead one astray with objects which are much larger or much faster. To (4): the use of a heuristic reshapes a problem, e.g. such that it becomes a problem of choosing from a smaller set of possible solutions.

Now, we turn to thinking about scientific discovery and theory generation.

5.2 Hypothesis formation and scientific discovery

Traditionally, philosophers have taken the view that the context of discovery[9] is not governed by any particular logic. Any particular method for dreaming up hypotheses is legitimate; the real question is whether the hypothesis in question can be justified on the basis of observation. Without taking any particular stance on the utility of visions of an ouroboros in one's fireplace, here I will follow Lindley Darden's work on discovery and hypothesis formation. Darden (1991) suggests that hypothesis formation may proceed legitimately, in some cases, from the use of scientific analogies. Analogical reasoning depends on finding ('retrieving') an explained phenomenon relevantly similar to the explanandum at hand such that one may legitimately appeal to causal patterns in the former to construct hypotheses about the latter. Darden (245) says that

> In Mendelian genetics, once one knows how to explain 3:1 ratios for a cross between yellow and green peas, that can serve as an exemplar (a close analog) for explaining a cross between tall and short peas or between red-eyed and white-eyed fruit flies.

In other words, the dominant/recessive explanation for the particular ratios in crosses of yellow and green peas allows one legitimately to hypothesize that a similar effect is at work in other reproductive outcomes. Once one has a general schema (as Darden calls it) for the phenomena in question, one can legitimately search for specific instantiations of this schema in the phenomena. In other words, one uses well-explained phenomena to guide hypothesis formation about the explananda. (Analogical reasoning is not, of course, the *only* legitimate means of hypothesis formation.)

Analogical reasoning of this sort is prevalent in science. Nyrup (2018) points to three broad ways that philosophers of science have defended the use of analogical

[9] I do not claim that there are perfectly separable contexts of discovery and justification; I just need a toehold for the distinction between theory generation and theory choice, cf. Okruhlik (1994).

reasoning: theory generation of the sort that Darden describes here, theory justification, and theory pursuit (i.e. development and investigation). In other words, philosophers have advocated the use of analogical reasoning in the contexts of discovery, justification, and pursuit, respectively. In the context of pursuit, analogies with some scientific problems may lend plausibility to particular solutions for other scientific problems. Similarly, although she does not use the language of pursuit here, Darden (1991) (247) notes that analogies provide a "weak form of plausibility" for new hypotheses, in that a hypothesis "constructed by analogy to a known...process" is more plausible than a hypothesis relying on some wholly new causal schema.

5.3 The mismatch heuristic

We now have a general picture of how heuristics and analogical reasoning can be used in science. Like other heuristics, the mismatch heuristic I propose can be used to identify particularly-plausible hypotheses for investigation. In using mismatch as a heuristic for discovery and pursuit, we employ analogical reasoning. In other words: the mismatch heuristic is the use of an evolutionary analogy to form hypotheses about the proximate causes of health outcomes.

Given that the desired outcome of this analogical reasoning is not an explanatory hypothesis *per se*, the move requires justification. I describe in turn two *justificatory* analogies for this move: epidemiological hypotheses about health outcomes and evolutionary hypotheses about fitness outcomes. Although the focus of the paper is of course *evolutionary* medicine, the epidemiology analogy seems usefully similar. I take it that these two analogies, taken together, show that the mismatch framework is *prima facie* reasonable as a method for hypothesis generation. In other words, analogical reasoning is involved at two points. First, we reason from evolutionary premises to health hypotheses: we treat the latter as analogous to fitness hypotheses. Second, we justify that move by appealing to its close similarity to ordinary reasoning within both epidemiology and evolutionary biology.

Per Broadbent (2013), epidemiology is concerned with explaining the "distribution and determinants of disease" across populations. In other words, epidemiologists investigate the population-level frequencies of various forms of morbidity, and also examine the distribution of causes of morbidity. In particular, epidemiologists often look at putative environmental causes of morbidity and mortality. For example, an epidemiologist might examine the relative frequencies of handgun ownership across populations and seek to determine the presence or absence of a correlation with relative suicide rates. If handgun ownership is associated with a higher suicide rate, then handgun ownership would be considered a 'risk factor' for suicide. The Framingham Study is particularly well known for identifying a variety of risk factors for cardiovascular disease. (Kannel et al. (1964), Krieger (2011): 150-156)

Epidemiological hypotheses, then, will often involve three key factors: a population, a health outcome, and a putative environmental cause of the health outcome in question. Note the similarity here to a mismatch hypothesis. A mismatch hypothesis will generally claim that *change* in an environmental character—say, the availability of 'cheap' energy—has resulted in a change in health outcomes—an

increase in, perhaps, metabolic syndrome. If we take an inference to be broadly legitimate in epidemiology when it moves from the conjunction of changes in disease distribution and changes in environmental characters to a hypothesis about particular causes, then it seems that a similar method for hypothesis formation using a mismatch framework ought also to be seen as broadly legitimate. In other words, the mismatch framework is sufficiently similar to ordinary epidemiological reasoning that acceptance of the latter licenses (at least) tentative acceptance of the former.

Naturally, disease-environment correlations do not automatically license the conclusion that a particular environmental character is the cause of a change in disease distribution in either epidemiology or evolutionary medicine. Rather, both frameworks—mismatch and epidemiological—can properly motivate the investigation of particular mechanistic causes, of possible interventions, and so forth. At the very least, someone who objects to the mismatch framework but not a broader epidemiological methodology owes us an argument.

One might worry that I conflate here so-called 'causes of cases' and 'causes of incidence', as coined by Rose (1985): the causes of a particular patient's illness and the causes of the distribution of that illness in a population. This need not be the case. That e.g. myopia may be far more prevalent in industrialized societies than agricultural societies due to an increase in close-in work, even if true, does not automatically license the conclusion that Jones has myopia because she is a software engineer. In making this argument, I am suggesting something like what we see in e.g. Koeth et al. (2013). They argue that human gut bacteria metabolize L-carnitine (a compound prevalent in red meat) such that the risk of cardiovascular disease (CVD) increases. The paper explicitly notes the observed association between CVD and red meat consumption in industrialized societies, and further notes that the previously-assumed culprit—saturated fat in red meat—does not appear to be associated with CVD. In other words, they use two major epidemiological findings in an attempt to drill down and identify a specific causal mechanism for the observed association. Note: their proposed explanation (if correct) does not entail that Smith personally suffered a heart attack due to his overfondness for bacon—only that the phenomenon's prevalence at the population level is explained by the mechanism. Identifying the causes of cases is a tricky business well beyond the scope of this paper, and here instead I focus on causes of incidence.

Let us now examine the evolutionary analogy. Consider again Darwin's example of deer and wolves. In this case, some deer are faster than others, and pass on their speed to their offspring. Those deer are more likely to evade wolf predation and, consequently, over the generations their offspring will make up a larger proportion of the population. (Naturally, there could be corresponding selection for speed in wolves.) Mean fleetness of the population as a whole will tend to increase. If the environment suddenly changes, however, such that speed is no longer an advantage—say, due to an invasion by ambush predators—the population may evolve differently. In this changed environment, perhaps selection will now work most strongly in favor of variants more attuned to the scent of their predators.

In this example, environmental change alters the fitness of particular variants within the deer population. As in the epidemiological case above, we consider an environmental factor, a population, and a particular *fitness* outcome. This is, of course, the basic form of an ordinary mismatch explanation.

A mismatch hypothesis about health, then, is an attempt to explain a health outcome like myopia as the result of a changed selection environment: due to changes in selection pressures relative to the EEA, certain traits become disadvantageous and result in negative health outcomes. As I explain below, the evolutionary reasoning which grounds this hypothesis may be wrong, but it is likely to be *useful*: it directs our attention to changing health-salient features of the environment.

The mismatch framework's structural analogies with epidemiological and evolutionary hypotheses give it some intrinsic plausibility. Note an additional analogy: in both epidemiological explanations and mismatch health explanations, the same basic outcome (health) is of interest. In a conventional evolutionary explanation, fitness is the outcome of interest. This need not do away entirely with the analogy, however: many physiological and psychological outcomes will be both fitness and health effects; indeed, health effects are likely necessary for many kinds of fitness effects to obtain. Thus, while mismatch hypotheses about fitness have an explanandum distinct from that of mismatch explanations about health, the phenomena of interest will often overlap. This is the fourth of the criteria from Wimsatt (2007) above: it transforms a problem (explaining observed health effects) into a related problem (explaining putative fitness effects). This, too, bestows plausibility on mismatch explanations of health outcomes.

The core difficulty on which the paper is focused remains, however: sometimes, fitness and health do not track each other, and in those cases a conventional mismatch explanation seems inadequate for understanding a particular health outcome.

I propose that with respect to health outcomes, we treat this mismatch framework as a heuristic: we use the framework to shrink the search space so that our attention is directed to plausibly salient features of the environment (evolutionarily-novel features, here), and we use the framework to identify particular live hypotheses which are worth pursuit. In the old parlance, then, we can use the heuristic as a discovery heuristic and a pursuit heuristic.

I do not suggest merely that we ought first to look at mismatch explanations for particular health effects and then, finding no fitness effect, discard the mismatch framework. Instead, I suggest that the mismatch heuristic can direct our attention to particular features of the environment—evolutionarily novel features of the environment (or features discordant with the optimal environment, following Morris (2018))—which we can then test for causal relevance. In other words, we can use the framework of ultimate explanations as a heuristic to identify possible proximate explanations, while recognizing that the ultimate explanation implied by the mismatch heuristic—while plausible—may be wrong.

The idea that an evolutionary perspective can have heuristic value for medicine is not original to this paper. Nesse (2008) (425) explicitly argues this. I go beyond Nesse in arguing that treating mismatch as a heuristic can help resolve the fitness-health tension inherent to so much of mismatch research. In particular, I allow that the correct ultimate explanation for a given health outcome caused by a novel environment may not involve mismatch at all; my particular concern is whether that mismatch framework helps us to develop useful clinical and public health interventions. To the extent that the mismatch heuristic directs our attention to interesting hypotheses about proximate (i.e. environmental rather than evolutionary) causes, it succeeds. If, when the dust settles, the health effect in question also appears to

involve a fitness effect, then so much the better. In that case, we need not merely treat the phenomenon *as though* it were a case of evolutionary mismatch; it would, *in fact*, be a case of evolutionary mismatch.

Why use the mismatch heuristic at all? For at least two reasons: first, as Lloyd et al. (2011) say, we know that human environments have changed tremendously in the last few millennia; second, certain diseases seem characteristic of exactly those populations whose environments have changed the most. In other words, rather than searching through all conceivable environmental causes (a rather large problem space), we shrink the problem space down to a more manageable size by looking first at the evolutionarily novel factors. We may not know if every environmentally-caused negative health effect is a result of evolutionary mismatch, but we know that it is the sort of effect which could be caused by mismatch.

Consider now this brief sketch of how one might employ the mismatch heuristic:

1. A particular health outcome is believed to be caused by environment (due, perhaps, to a rapid increase in its prevalence).
2. This particular outcome seems not to show up in ancestral human populations, e.g. contemporary hunter-gatherers.
3. The researcher turns her attention to focus particularly on those environmental factors which most strongly break from the EEA, either carving off those parts of the search space which do not involve evolutionary novelty, or—if live hypotheses already exist—pursuing those which fit into a mismatch framework.

I take it that an accommodating shrug is all I require from those who think that discovery, unlike justification, is ungoverned by normative considerations. For those who think, following e.g. Langley et al. (1987) (54), that scientific discovery requires us to evaluate the heuristics we use, allow me to dally a bit longer on the analogical reasoning to which I appeal. Recall that (as discussed in section 5.2) analogies can lend plausibility to new hypotheses. Recall, further, that I have pointed to analogies between (1) the mismatch heuristic and ordinary evolutionary explanations, and (2) the mismatch heuristic and ordinary epidemiological explanations. Both analogies involve a similar explanatory structure concerned with the impact of environmental changes on populations in those environments. The nature of the impacts—fitness and health, respectively—are overlapping (and likely broadly correlated) but distinct. Given the close analogy between these types of explanations and the similarity between the outcomes of interest, the mismatch heuristic lends some initial plausibility to the hypotheses it helps us to generate—assuming, of course, that in using the mismatch heuristic researchers appeal to genuine environmental differences.

The mismatch heuristic succeeds when its evolutionary framework directs our attention to correct proximate explanations. The mismatch heuristic fails when it directs our attention to incorrect proximate explanations—particularly when those proximate explanations are uncorrelated with correct explanations. All heuristics fail sometimes, of course, and per Wimsatt (2007) above a given heuristic should fail in ways characteristic of that heuristic. When, then, should we expect the mismatch heuristic to fail? The mismatch heuristic leads us astray, first, when we naïvely assume that plausible evolutionary explanations are good enough to give us health explanations. The heuristic leads us astray, second, when the correct explanation involves fitness-neutral environmental changes *and* the wrong proximate explanation is selected. In other words, the mismatch heuristic characteristically

fails us when we have selection-irrelevant environmental changes which distract us from the correct explanation.

5.4 Advantages of the account

Mismatch concept agnosticism: an advantage of this account is that it does not require debating what mismatch, as a biological phenomenon, actually is. (Lloyd et al. (2011), Garson (2015), Cofnas (2016), and Morris (2018) all discuss this in more detail.) I intentionally do not consider whether 'real' mismatch is a fitness-only phenomenon, or also a health phenomenon. Solving that problem is of course a worthy endeavor, but the nature of mismatch as an evolutionary phenomenon need not be resolved before mismatch can be used responsibly in clinical research and practice. This is particularly important given that we might reasonably question whether humans experience decreased fitness in contemporary environments: if the population growth rate has increased after the dawn of agriculture, then it seems mismatch has decreased. This problem for mismatch has been discussed by, e.g., Méthot (2011, 2015), and my approach here sidesteps the worry.

Health concept agnosticism: a related advantage of this account is that we need not have a fully worked-out picture of what it means for a physiological or psychological state to be a state of health or disease. The ultimate goal of the account is finding proximate explanations for outcomes of interest. That practitioners take some outcomes to be healthy or diseased may help explain their interest in an explanation, but it does not play a role in the mismatch heuristic itself. Thus, this provides a pragmatic response to well-defined-but-unsettled battle over naturalist vs. normativist health concepts.[10] As long as we can identify particular physiological or psychological outcomes of interest, we need not have a unified picture of what 'counts' as health or disease.

5.5 The problem space

Now that we have seen both the basic account and some reasons to like the account, let us circle back to a question the reader may have. To this point, I have talked a fair bit about using the mismatch framework to shrink the problem space to be searched. I have not yet explained how to generate the problem space.

One way we might think about this: the problem space is 'out there' already, in the sense that (perhaps) there is just a fact about what specific sequences obtain in all possible chess games. In that same sense, all possible proximate causes of a given health outcome are out there to be searched, and the mismatch heuristic simply directs our attention to the evolutionarily salient ones. I find this answer to be unduly fuzzy, however—not least because it is not clear a problem space is already waiting for us to search it. After all, part of the reason for heuristics in chess is that we simply *cannot* generate the problem space and then search through it.

[10] Since it is the best-defined part of the dispute, I refer here to the debate between what Kingma (2014) has called Domain II naturalism and Domain II normativism. The mismatch heuristic is agnostic with respect to disputes in the other domains she identifies as well.

Fortunately, Simon and Newell (1971) have a suggestion for us: one source of information for generating problem spaces is our "previous experience with analogous tasks" (155). In other words, when we recognize that we face a problem related to a previously-explored problem, we can use a similar problem space. What is our problem space here, then? It seems that the most obvious answer is the sum of epidemiological and anthropological knowledge of human environments (broadly construed to include culture, lifestyle, and so forth). When we suspect that a negative health outcome is caused by the environment, then, we know that our problem space is—at an outer bound—human environments. (Realistically, when attempting to generate hypotheses this can be narrowed to actual *knowledge* about human environments, not human environments broadly.)

Once we have our problem space mapped out, which gives us our set of possible environmental factors to explore, we can apply the mismatch heuristic. The evolutionarily novel subset of total environmental factors to which humans are exposed comprises the post-heuristic problem space to be searched. One might imagine, if the reader will pardon the colorful illustration, a grille cipher: our 'encrypted' message is the problem space, or a list of environmental factors to which some humans are exposed. Our cipher's cut-outs appear only over evolutionarily novel environmental factors, thus reducing the search space to the 'decrypted' message. (In practice, of course, the search would involve a mix of qualitative and quantitative analysis of the sort regularly used in epidemiological research—attempting to identify correlations among health outcomes and environmental variables identified as evolutionarily salient.)

5.6 Viability for research programs

It is worth reiterating at this point that the intent of this paper is not to lay out a comprehensive case for the usefulness of mismatch thinking in medicine. Instead, I have pointed out a problem in mismatch thinking—the fitness-health tension—and proposed a solution for the problem. In other words, I have sought to ensure proper conceptual housekeeping among evolutionary medicine researchers. If someone is inclined to view mismatch thinking unfavorably (at least with respect to its use in medicine), I have not tried to convince her otherwise. In particular, I have not tried to convince such a person that she should surrender heuristics she has found fruitful in her own research—not least because there is no reason to see the mismatch heuristic as excluding most or all other heuristics. (The causation-detection heuristics in Hill (1965), for example, ought to be entirely compatible with the use of the mismatch heuristic.)

With that caveat, there is some reason to think that mismatch thinking has been scientifically fruitful. Although they do not use the term 'mismatch', Eaton and Konner (1985) clearly employ mismatchy thinking when they point to dietary changes in pre- vs. post-agricultural societies to explain the presence of the so-called "diseases of civilization". Neel (1962), in proposing his famous "thrifty genotype" hypothesis, similarly points to environmental change in modern societies relative to "primitive" societies as a causal factor in the recent rise of diabetes rates. Both papers have earned considerable follow-on research, clinical trials, and

so forth.[11] The presence of active research programs to evaluate these mismatch hypotheses is strong *prima facie* evidence of the mismatch heuristic's utility.

6 Taking stock

I have argued that evolutionary mismatch explanations of health and disease can conflate fitness and health. To resolve this tension, I have proposed the use of mismatch as a heuristic to reduce the size of the problem space to be searched, such that researchers can zero in on evolutionarily novel environmental factors. At this stage, the hypothesis is actually a proximate hypothesis which needs to be tested like any other.

The goal of this paper has not primarily been to convince the skeptical reader that evolutionary mismatch research is valuable. That would require far more space than I have here. Instead, I have tried to show that the mismatch heuristic can be used without running aground on the shoals of conceptual confusion.

Acknowledgements Special thanks to Roberta Millstein (University of California, Davis) for extensive feedback on previous drafts of this article. Thanks also to the audience of the American Association for the Advancement of Science Pacific Division's 2018 conference, particularly Bert Baumgaertner (University of Idaho).

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[11] For a small sample of research inspired by work on Paleolithic nutrition, see e.g. Lindeberg et al. (1997), Eaton et al. (1999), Lindeberg et al. (2001), Lindeberg et al. (2007), Lindeberg (2010), Whalen et al. (2016), Whalen et al. (2017), Manousou et al. (2018).

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