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Unpacking the heritability of diabetes: The problem of attempting to quantify the relative contributions of nature and nuture

Author
Chaufan, Claudia, MD, PhD

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Unpacking the heritability of diabetes: The problem of attempting to quantify the relative contributions of nature and nurture

Claudia Chaufan, Institute of Health & Aging in the School of Nursing
University of California, San Francisco; e-mail: claudiachaufan@yahoo.com

In this paper I analyze the concept of heritability as used technically in medical research. I use diabetes as a paradigmatic "common disease" whose heritability is computed with a view to disentangling the relative contributions of "nature" and "nurture". I show what heritability measures and what it does not, and theorize about the scope of application of this measurement for diabetes-relevant medical research, health care practices, and public health policies. I argue that this analysis applies to heritability studies of comparable diseases and complex phenotypes, concerning which heritability estimates shed little if any light on the nature-nurture question, and provide no information relevant to medical practices and public health policies that we do not already have. I conclude that what is interesting about heritability studies in diabetes and similar human contexts is not what they tell us, or fail to tell us, about the relationship between nature and nurture, but what they show about the social and political nature of the practice of medicine and behavioral sciences.

Keywords: heritability, nature-nurture debate, type 2 diabetes, social determinants of health

I propose to show […] that a man's natural abilities are derived by inheritance […]. As it is easy…to obtain by careful selection a permanent breed of dogs or horses gifted with peculiar powers of running, or of doing anything else, so it would be quite practicable to produce a highly gifted race of men by judicious marriages […]. The arguments by which I endeavour to prove that genius is hereditary, consist in showing how large is the number of instances in which men who are more or less illustrious have eminent kinsfolk.

Francis Galton, Hereditary Genius, 1869, 11; 15.

Many articles have been devoted to the likely value of the heritability of intelligence. The present article focuses on the concept of heritability itself and questions its intelligence. Heritability analysis […] has become the dominant paradigm in academic psychology and now appears prominently in introductory texts, where it is presented to naive students who have no understanding of the false assumptions inherent in the calculations. This preeminence of heritability analysis is the outcome of a power struggle, not the resolution of a debate among scientists.

***D*ouglas Wahlsten,**
The Intelligence of Heritability, 1994

Introduction

Over thirty years ago, population geneticist Richard Lewontin contended that researchers should "stop the endless search of estimating useless quantities" (Lewontin 1974, 410). He was referring to studies quantifying the heritability of complex human phenotypes, and argued that these studies needed to stop given "the terrible mischief that has been done by confusing the spatiotemporally local analysis of variance with the global analysis of causes" (410) (Phenotype is any morphological, functional, or behavioral characteristic of an organism, and contrasts with genotype, an organism's DNA). Lewontin viewed as one such "mischief" the quest to quantify the heritability of intelligence, or rather, intelligence quotient (IQ), which had led the prestigious Berkeley psychologist Arthur Jensen to conclude that African Americans were, on average, less intelligent, for genetic reasons (Jensen, 1969). Of course Lewontin did not view what he called a "useless" enterprise as a mere mishap on the part of researchers, but one animated by political reasons, at least in some cases.

In this paper, I apply Lewontin's analysis of heritability to one complex human trait, type 2 diabetes (hereafter diabetes), a disease whose rates are increasing epidemically, whose consequences are disabling when not lethal, and which affects disproportionately ethnoracial minorities, immigrants, and the socially excluded. Researchers have sought to estimate the heritability of diabetes in the belief that this measurement will shed light on its genetic causes and help disentangle them from environmental contributors to the disease. This in turn should lead to novel treatments, or to personalized treatments, i.e., tailored to individuals' genetic makeup.

I examine closely one heritability study that I use as a model of heritablity studies in diabetes generally. I take diabetes to be a paradigmatic common disease, as these diseases are defined by the medical literature (King, Rotter, and Motulsky, 2002), and as an exemplar of complex, polygenic and multifactorial human traits generally. I explore various interpretations of heritability and conclude that heritability estimates shed little if any light on the relative contributions of "nature" (i.e. genes) and "nurture" (i.e. environment) to the diabetic state, and that these estimates provide no information relevant to diabetes-related medical practices and public health policies that we do not already have. My analysis should also apply to heritability studies, medical practices and public health policies concerning diseases comparable in their pathophysiology and etiological complexity. I will suggest that what is interesting about heritability studies in diabetes is not what they tell us, or fail to tell us, about the alleged genetic roots of diabetes, but what they show about the social and political nature of the practice of science, and about the marriage of interests between the research, the policy, the corporate, and even the non-profit sectors, which I have discussed elsewhere (Chaufan, 2007).

I am fully aware that my point about the limitations of the concept of heritability has been repeatedly made, and brilliantly so, for mental health and cognitive abilities (Block and Dworkin, 1976; Joseph, 2006; Lewontin, Rose, and Kamin, 1984). However, and maybe because conditions such as diabetes are less open to controversy than cognitive abilities or behaviors, claims and arguments that otherwise invite controversy (e.g. about a "genetic predisposition" to "criminal behaviors"), go unchallenged all too frequently when applied to diabetes. My analysis attempts to address this gap.

Background

Since World War II rates of diabetes have skyrocketed, leading to talk of an epidemic, believed by many to result from presumably adaptive genotypes colliding with the lifestyles of affluent postindustrial societies – largely their food excesses and physically undemanding jobs (Bernstein, 2000). Diabetes has been described as the "epidemic of the new millenium" (Jovanovic, 1999), and with good reason. First, if left untreated or if poorly treated, it leads to disabling complications and to premature death. Second, rates have increased dramatically over the last fifteen years, the increase is global, and its projected distribution is very uneven. Conservative estimates indicate that by the year 2025, the number of people affected by diabetes will rise to 333 million (from 135 million in 1995), an increase of 42% in the developed countries, yet of 170% in developing countries; and while these numbers do not discriminate among types of diabetes, at least 90% of the cases are presumed to be type 2, the real protagonist of the epidemic (King, Aubert &Herman, 1998). Third, diabetes is very costly: in the United States alone, it now imposes an annual toll of over 130 billion dollars, including direct medical and indirect productivity-related costs – one out of every ten health-care dollars (King, Aubert &Herman, 1998). Last, rates of diabetes and diabetes complications are two to six times higher among minorities worldwide

than among dominant groups (King, Aubert &Herman, 1998).

The struggle between genes and environment is central to public debates on the diabetes epidemic: it drives the interest in understanding nature and nurture's relative roles (Taylor, 2004) and the attempts to measure the heritability of the disease, estimated to range from 55% to 100% (Newman & al, 1987), although studies using twin registries rather than clinical samples have suggested numbers lower numbers, around 20 to 30 % (Kaprio et al., 1992). These numbers are believed to provide "information regarding the relative importance of genetic and environmental factors in the etiology of diabetes" (Kaprio, et al, 1992, 1060). Yet because estimates are rarely 100%, and because diabetes responds to environmental interventions, researchers have concluded that "non-genetic factors may also influence diabetes development" (Newman et al., 1987, 763), and a debate has emerged between those who emphasize its genetic component and those who emphasize what are conceptualized as "environmental triggers", largely eating and exercise habits (Chaufan, 2006).

Yet all researchers agree that genes *and* environment, nature *and* nurture, *combine* to cause the disease, whatever their disagreements over relative weights. Researchers also agree that diabetes is anything but inevitable, and that the current increase in rates could be greatly reduced, when not eliminated, by minimizing well-established environmental contributors (Zimmet, 2003). All the same, it is believed that knowledge of the heritability of diabetes should help isolate the contribution of genes to the disease (Katoh et al, 2005) which, once known, could be intervened upon selectively, for example, by developing pharmaceuticals tailored to genetic makeup (Gloyn, 2003).

Some preliminary considerations

Before I begin exploring the concept of heritability, some methodological considerations concerning heritability studies are in order. What conditions need to be met to measure the heritability of any trait, and to apply this knowledge to some practical purpose? Attempting to answer this question will give us the chance to review the considerable knowledge we already have of the causes of diabetes. It will also supply us with reasons, additional to the conceptual weaknesses of heritability which are our main concern, to question the continuing preoccupation with heritability in diabetes and other areas in the human sciences.

Jay Lush, the father of modern scientific animal breeding, defined heritability in the 1940s as "the fraction of the observed or phenotypic variance […] caused by differences between the genes or the genotypes of the individuals," represented by the formula:

$$H^2 = \frac{Var\ (G)}{Var\ (P)}\ .$$

Lush stated clear conditions for its estimation and a clear goal for measuring it, believing that that the inability to "identify and describe the genes individually" was almost "no handicap" for breeders of "economic plants and animals" (Lush, 1949, p. 357) intending to select for desirable traits -- for instance, to raise cattle with high milk yield -- because heritability estimates would guide their choice of specimens exhibiting the desirable traits or phenotypes under well defined environments.

"To know that heritability is low and high", stated Lush, "is important when making efficient selective breeding" of well specified traits. Lush noted that "since heritability is a ratio, its value can change as either the numerator or the denominator changes" (357), and warned breeders that unless they measured the environmental term accurately – the importance of which he deemed "obvious" (367) -- the results of their estimates would appear "contradictory" (358). "If a character can be

influenced strongly by environmental variations", noted Lush, "its heritability would be low in a population in which the environment varies widely", yet high in one where variations were minimal (358). Accurate heritability estimates of a well defined trait calculated under well measured environments, concluded Lush, would guide breeders' selective crossing of specimens and help them achieve their goals.

In contrast, when attempting to measure the heritability of traits in humans, it is far from clear that the conditions Lush states for an adequate estimate can be met, or that comparable goals can be claimed, for methodological, empirical and ethical reasons.

First, how do we operationalize human phenotypes, be it diabetes, smoking, shyness, religiousness, or criminality, all traits whose heritability has been estimated (Arbelle & al., 2003), with the same precision as we measure milk yield per cow? Here, diabetes researchers have an advantage over psychological and behavioral researchers: they can use recognizable biological indicators of diabetic states, such as insulin or glucose levels, develop techniques to measure them, such as oral glucose tolerance tests or euglycemic-hyperinsulinemic clamps, and agree on which numbers will be considered sufficient for diagnosing diabetes. It gets trickier with psychological traits, and worse still with "predispositions" and "tendencies".

Second, how do we determine which environments are relevant to the phenotype of interest *in the full course of its development* with a precision comparable to that which plant and animal breeders can achieve? Fortunately, in diabetes we do have a fairly good knowledge of these environments and good evidence that they influence glucose tolerance, i.e., the ability or lack thereof to metabolize glucose, and thus affect the genesis of diabetes, almost from conception and throughout the life course.

For example, it is well established that both poorly controlled diabetes during pregnancy (Freinkel, 1964, 1980; Jovanovic and Pettitt, 2001) and maternal malnutrition (Barker, 2003) impair the development of the fetal pancreas and sensitivity to insulin generally later in life. Studies showing that fetuses responded to their diabetic mothers' high blood glucose levels by increasing their own secretion of insulin (Dabelea & al. 1998), and a seminal study conducted during the Dutch famine in WWII (Ravelli & al, 1998) showing that individuals born to mothers who had experienced hunger during key periods in the development of the pancreas were insulin resistant have been interpreted as indicating the effect of "fetal programming", that is, as causing "a permanent or long-term change in the structure or function of an organism resulting from a stimulus or insult acting at a critical period of early life" (Barker & Osmond, 1986, 596).

It is also well established that the effects of malnutrition on development do not stop at birth, but continue into the very first years of life. Stunting, the failure to thrive due to lack of basic nutrients in early childhood, currently impairs the adequate metabolic development of some 200 million children worldwide and predisposes them to heart disease, obesity, and diabetes (Branca & Ferrari, 2002), independently of ethnicity (Popkin, Richards, & Montiero, 1996), not merely in industrializing countries but also in such wealthy countries as the United States, where at least 12 million children are at risk of hunger (Koch, 2000).

Additionally, that the role of environment in the developmental origins of insulin resistance transcends any single generation is supported by a wealth of experimental and observational data: animal experiments have shown that insulin resistance can be transmitted, even amplified, non-genetically, over several generations of rats exposed to nutrient-deficient or hyperglycemic uterine environments during the fetal stage, and to diets of varying composition over the life course. These experiments demonstrated that,

when compared to a control group (from the same breeding colony, hence with minimal genetic variability), specimens born to mothers malnourished while pregnant were small at birth and became glucose intolerant as young adults. When these adult females themselves became pregnant, they "passed down" their glucose intolerance to their offspring even when they and their offspring consumed nutritionally adequate (control) diets. The glucose intolerance (and accompanying insulin resistance) of this younger (F2) generation was also extremely refractory to dietary manipulation (Benyshek, Johnston, & Martin, 2004). More recently, rat experiments have extended this multi-generational effect to the grand-offspring (F3) of the first experimental generation (Benyshek, 2006).

The multi-generational, non-genetic transmission of glucose intolerance and insulin resistance offers a persuasive explanation for the staggering rates of diabetes among Native, and arguably other high prevalence, populations worldwide (Benyshek, 2007). Hence Benyshek, et al. (2001) examined the combined nutritional and socio-political history of several high prevalence Native American populations, including the Pima of Arizona, showing that tribal members were often subject to cycles of severe malnutrition in the early reservation period during long marches and forced relocations between 1870 and 1940. After World War II, this period of extreme privation was followed by higher wages and welfare nutrition programs, which increased calorie intakes and exposed underlying insulin-resistant states produced by widespread and significant malnutrition during previous decades. Incidentally, this explanation challenges Neel's now classic "thrifty gene theory", which suggests that the disproportionately high rates of diabetes among ethnoracial minorities is due to a combination of selective pressures and genetic differences (Neel, 1962). Yet the selective evolutionary pressures hypothesized by the theory contradict historical and anthropological findings (Benyshek & al, 2001), and "diabetes genes," arguably the main assumption of the theory, remain, in the words of one genetic researcher, elusive (Gloyn 2003, 111).

In sum, the developmental origins of health and disease, grounded in prenatal, perinatal and early life, environmentally-generated perturbations leading to an increased biological (not genetic) predisposition in adulthood to a range of conditions, including diabetes, have been firmly established. Moreover, the evidence that these predispositions can be passed down to subsequent generations, and that at least in some cases the processes underlying this "inheritance" are social and political in origin, is growing (Benyshek, 2007).

Similarly, there is little, if any, disagreement that insulin sensitivity is affected by environmental factors at any age. The effects of high calorie diets and low levels of physical activity are well established, as it is well established that environmental ("lifestyle") changes can not only delay, but even prevent, the onset of diabetes, independently of ethnic (Tuomilehto & Lindstrom, 2003) or genetic (Siitonen, & al, 2004) backgrounds.

Finally, that the complications of diabetes are strongly responsive to environmental interventions is no longer a matter of debate, even if their heritability continues to be measured (Langefeld, & al. 2006). Dramatic reduction in the rates of chronic complications in both type 1 and type 2 diabetes, of up to 70%, have been achieved with intensive management of blood glucose in two major clinical studies conducted in North America (American Diabetes Association, 2002a) and in the United Kingdom (American Diabetes Association, 2002b) respectively, and there is reason to believe that genetic makeup made no difference. In fact, the North American clinical trial was interrupted earlier than planned to allow everybody to pursue the benefits of intensive, high quality diabetes care.

Thus we possess a fairly sophisticated knowledge about a range of diabetes-relevant environments and about the sensitivity of at least many genotypes to them. This surely gives reason to question the need for continued diabetes heritability studies. But, to return to our main concern, how are we to make use of this knowledge in arriving at diabetes heritability estimates? In human, as opposed to animal and plant, research, how exactly do we control all these environments, not merely statistically, but empirically, to estimate unbiased measures of the heritability of diabetes? Put otherwise, how can we make sure that the subjects of our studies have shared the same trait-relevant environments, enabling us to incorporate the necessary environmental variance information into our heritability estimates?

Twin studies: a natural experiment?

For present purposes, let us assume that we can overcome these methodological hurdles, and accept that the computation of the difference between within-group correlations of identical and fraternal twins achieves just that. After all, twin researchers in diabetes do not generally use the classic analysis of variance (ANOVA) formula to estimate heritability, which requires a calculation of environmental variance, but rather one based on the difference between within-group correlations of identical and fraternal twins (Kaprio, & al. 1992). This formula establishes that:

$$H^2 = 2\,(r_{mz} - r_{mz})$$

in which:

- H^2 = heritability,
- r_{mz} = correlation for the trait in monozygotic twins, and
- r_{dz} = correlation for the trait in dizygotic twins.

The environmental variance is assumed equal (or trait-relevantly equal.)

The latter formula demands only that the diabetes-relevant environments which identical and fraternal twins experience be, for all intents and purposes, "equal" (the trait-relevant Equal Environment Assumption or trait-EEA), requiring no more than minor adjustments with interaction terms. According to the reasoning, the difference in intra-pair correlations (in the case of continuously distributed traits such as fasting insulin), or concordance rates (in the case of categorically "yes-no" traits such as diabetes) between pairs of identical twins reared together (and so sharing the same environments) and pairs of fraternal twins reared together (so also sharing a same environments), so long as the two environments are relevantly equal, *has* to measure the heritability of the disease (ibid). This relation is represented by the formula:

Again, let us set aside the methodological reservations about twin studies, expressed by twin and genetic researchers themselves, who have overtly warned that these studies need to be interpreted with caution, because major assumptions underlying them, including, but not limited to, the trait-EEA, may simply not obtain (Hall, 2003). Let us also set aside how twin researchers themselves have unknowingly undermined this assumption by noting that food preferences (Breen, Plomin, & Wardle, 2006) and leisure-time levels of physical activity (Carlsson, Andersson, Lichtenstein, & Michaelsson, 2006) are more similar among identical than among fraternal twins. (Even if twin researchers hypothesize certain gene variants as "explaining" variations in eating and exercise patterns, it would *still* be either food intake or levels of physical activity -- arguably two diabetes-relevant *environmental* factors -- that *cause* diabetes, in any meaningful sense of the term "cause"). Last, let us set aside as well the reservation of critics of twin studies, who have argued that the assumption that fraternal and identical twins share equal environments,

relevant or not, is false (Lewontin, Rose, & Kamin, 1984) and that twin studies are no more than, in the words of one critic, pseudoscience (Joseph 2002).

In sum, let us assume that the EEA, or better still, the trait-EEA, is true. For current purposes, let us grant more generally that we can identify, and quantify, all relevant environmental contributors to diabetes, hence that its heritability in a human population can be measured. We are still left with the question, *what is the point of doing so*? Heritability studies in the human sciences cannot share a goal comparable to that of animal breeders, anything like "improving farm animals by suitable genetic methods" (Lush, 1949). Nor would one assume, at least in principle, that they share Francis Galton's goal, quoted in the epigraph, of improving the human stock. Surely, the *point* instead *has* to be the one suggested at the beginning, i.e., to illuminate the nature-nurture question concerning the etiology of diabetes in the hope of using this information to intervene selectively on the specific contribution of genes to the development of the disease.

We may assume that something like this must be what Katoh et al. had in mind when they set out to conduct a study to "illuminate the role of genetic influences in the pathogenesis of diabetes" (2005, 2642). The researchers assumed that a "greater concordance for type 2 diabetes among [identical] compared with [fraternal] twin pairs […] indicate an influence of diabetogenic genetic factors", hence their twin study (2642). Their hypothesis that such influence exists was allegedly confirmed by the finding that among the 156 twin pairs randomly selected from the Finnish Twin Cohort, the heritability of fasting insulin levels (an indicator of insulin resistance, a precursor of diabetes) was 43 percent.

So how should we interpret this statement?

It presumably claims that the ratio of genotypic variance to phenotypic variance - to requote Lush, "the fraction of the observed or phenotypic variance […] caused by differences between the genes or the genotypes of the individuals" - in the matter of diabetes is 43/100. But how are we to understand this claim?

What do heritability estimates show about the nature-nurture question?

One natural, if naïve, way of interpreting the statement would be to say that 43% of Katoh et al.'s *identified cases* of high fasting insulin levels are fully explained by genetic causes, while 57% of identified cases are explained by environmental causes.

But this interpretation cannot be correct, nor does any serious researcher suggest it is: they all seem to agree that diabetes results from *interactions* between "several altered genes" (Tusie Luna 2005, 211) and a range of environmental factors not in *some* but in *all* individuals who develop the disease (Freeman & Cox, 2006; Gloyn, 2003; Tuomilehto & Lindstrom, 2003). Moreover, when it comes to lifestyle changes, clearly an environmental factor, referred to as critical to prevent diabetes, Kato et al. underscore their importance and give no hint that their recommendations apply to some diabetic patients but not to others (2005).

Indeed, Katoh and al.'s emphasis on the importance of lifestyles is consistent with the clinical trials mentioned in the previous section, which have conclusively demonstrated that the onset of diabetes is not only delayed, but even prevented, by lifestyles changes in individuals of all ethnicities examined (Tuomilehto & Lindstrom, 2003). Moreover, gene variants statistically associated with diabetes may make no difference if lifestyle interventions are implemented, as indicated by one study reporting a variant of the ADRA2B gene, which predicted diabetes "in subjects with impaired glucose tolerance who [were] *not* subjected to a lifestyle intervention", yet failed to do so in those who were (Siitonen et al. 2004, 1416).

So again, how are we to interpret Katoh et al.'s heritability claim?

Should we take it to mean that, *for any given subject in their study* (or perhaps for the *average* subject?) with elevated fasting insulin concentration, 43% of it comes from their genes and 57% from diabetes-relevant environments -- what they have eaten and exercised over the course of their lives, their prenatal environment, and so forth? This reading *seems* to make sense.

Unlike the first naïve interpretation, it is compatible with, indeed presupposes, the fact that *both* genes and environment play a role in any metabolic function or dysfunction. Yet it then goes on to assume that the relative weights of both can be quantified. This assumption is not obviously false. When two factors jointly cause a given effect, one can often ask how much each of the factors contributes. For example, if a massive charged body is undergoing acceleration, it makes sense to ask how much of the acceleration is due to its mass (effects of the law of gravity) and how much is due to electrical charges (effects of Coulomb's law) (Sober, 1988).

But if we can say of one of Katoh et al.'s subjects that her diabetes is 43% due to her genes and 57% to her environment, we must be able to say something similar of any of her phenotypic traits, for instance, her height. The same subject's height too is clearly influenced by her genes and a historical sequence of environments relevant to her height encountered as she grew up (nutrition, childhood diseases, medications they may have taken or failed to take during critical periods of her growth). But from the acknowledgement of the contribution of both genes and environments to a trait, does it follow that we can meaningfully ask *what percentage*, or *how much* of this subject's total height comes from her genes and how much from her environment? Would it make sense to claim that if this person is five feet tall, 43% (roughly two feet) come from her genes and 57% (roughly three feet) from the sequence of environments contributing to this height? Or vice versa?

There is evidently a problem with attributing a percentage of anybody's height to genes and another one to environmental factors. And the problem is not in *which* numbers are attributed, but *in the very fact of attributing a number, any* number. Such an attribution makes no sense: it does not permit of truth or falsity. And the same is the case with fasting insulin levels or any other trait. It makes no sense to assert, or deny, that x percent of *someone's* diabetes (or shyness, or criminal behavior) is caused by her genes and the remaining 100 – x percent by the environments she has lived in. Why is this so?

Population geneticist Richard Lewontin has proposed the following, now classic example, that shows why heritability measures fail to answer the question of *how much* genes contribute to phenotypes, that is, to illuminate the nature-nurture question. If two bricklayers build a wall, one can calculate how much of the wall each worker built by counting the number of bricks each one added to it. In contrast, if two workers build a wall, one by laying the bricks and the other one by mixing the mortar, it would not make sense to quantify their relative contributions by measuring the volumes of bricks laid and mortar mixed (Lewontin, 1974). The two workers' contributions are not independent of each other. Therefore, there are no common units to measure how much of the wall each worker "caused".

Of course one could decide that what matters is the number of hours each worker put in, or adjudicate a value to their respective tasks (whether bricklaying or mortar mixing) and make these relevant to compensation, such as economists do, but these would not be measures of *how much* of the wall each worker helped bring into being. Rather, it would reflect our subjective judgment about the worth of different tasks.

Likewise, genes and environments do not build phenotypes independently of each other, and there is no common unit of measurement that enables us to say that *in one*

individual her genes made a 43% contribution to some trait, while the environment contributed 57%. The *appearance* of sense is a rhetorical illusion. In the acceleration of a massive particle, gravitation and electrical forces do operate independently of one another. Units of force do provide a common currency for stating their relative contributions. In contrast, organisms and their phenotypes are the *non-additive* product of genes, a historical sequence of environments, and developmental random noise, and the interdependence of all three precludes any meaningful quantification of the "ingredients" that go into the mix (Lewontin, 2000).

This is why the claim that 43% of somebody's fasting insulin levels (or height) comes from their genes and 57% from the sequence of environments relevant to it in the course of its development is nonsense - literally.

Unpacking the concept of heritability

So Katoh et al.'s heritability measure of diabetes as 43 percent cannot intelligibly be read as claiming that for each, or for the average member of the population studied the contribution of *her* genes to *her* diabetes is 43 percent. Indeed heritability in its technical sense is an attribute, not of the traits of individuals but of *traits in a population.* As indeed Katoh et al. are well aware, "heritability is a population-specific characteristic that has *no interpretation on the level of the individual or the family*" (2644, emphasis added). So the question remains: what does 43% heritability in fasting insulin levels mean, and what exactly is it a measure of?

As stated above, the formula to estimate heritability essentially quantifies how much *variations* in the genomes of a *given* population (with a certain genetic background and distribution of genotypes) under a *given* range of environments relevant to the development of the trait being studied explain, statistically, variations in the trait. In the study by Katoh et al mentioned above, for instance, it quantifies what percentage of the *variations* in fasting insulin concentration in *their* population of 156 twin pairs (with a specific genetic background and distribution) exposed to whichever environments were relevant to the development of *their* diabetes up to the moment when their fasting insulin levels were measured (assuming these environments were properly factored into the equation) is explained, *statistically*, by variations in the genotypes of *that* population (estimated by subtracting the intra-pair correlation of rates of insulin secretion of identical twin pairs from that of fraternal twin pairs). Thus it is correct to claim that the heritability of fasting glucose concentration *in Katoh et al.'s* sample is 43%.

Yet change the size of the sample (from 156 twin pairs to any other number), or the type or relative composition of genotypes in the population (156 *different* twin pairs), and the estimate will change. Change the range of environments under which those genotypes were studied, and the estimate will change as well, even when, clearly, the diabetes and insulin resistance *of each patient* have not changed. As Lush specified, change any of the variances, whether the type or relative frequencies of either genotypes or environments, and the heritability of the trait will change because heritability is an estimate of the relative contribution of genotypic *variance* to total phenotypic *variance*, *not an analysis of the causes of the trait*.

If genes and environment did not interact, then the proportion of variance associated with a change in relative frequency of genotypes and the proportion of variance associated with a range of environments, would, in fact, be the same as the proportion of the effect associated with each cause. Yet as mentioned above, genes and environments do interact, in complex, non-additive ways, to produce the phenotype, hence their relative contributions, like the case of the two workers contributing either bricks or mortar, cannot be

estimated, not even "approximately", because there is no common denominator.

So the problem with the heritability measured by Katoh et al. is that it is not an estimate of what everybody would like it to be: is not a *global analysis of causes* or of biological functional relationships, an estimate of *how much* of a persons's diabetes is caused by her genes. Rather, it is *a local, spatiotemporal analysis of variances* (Lewontin, 1974), an estimation of how much of the genetic variation in a specific population of a specific genetic composition and distribution exposed to a historically specific sequence of environments explains, statistically, that population's phenotypic variability. The problem cannot be "resolved" by collecting *larger*, or *more representative*, samples, by conducting *more* heritability studies, or by *supplementing* heritability estimates with additional data, because heritability is *irrelevant* to the pathophysiology of fasting insulin itself. And if something is irrelevant to an issue, no additional evidence can make it relevant.

This is why heritability estimates are useful in agriculture and farming, where environments can be manipulated to breed well specified, desired traits, and useless in humans, where this manipulation and selective breeding are not possible, not only for ethical reasons, as generally agreed in our day, but also for empirical ones. Moreover, in medical research the goal is clearly *not* to weed out "bad" genotypes and select the "good" ones to produce "desired" traits in the *given* or *available* environments. Rather, diabetes researchers, and health researchers more generally, seek to produce knowledge about disease states that may help medical professionals develop and administer the best interventions *to the patient population they have*, inform preventive strategies effective for the greatest number of human genotypes, shed light on which environments will allow human health to flourish, and advocate for them if at all possible, all this illuminated by the wealth of knowledge already available about the developmental origins of insulin resistance and of disease more generally.

And, as described above, at least in diabetes it is already well established which environments are optimal if the goal is to *reduce*, rather than increase, the heritability of diabetes, and it is not genetic makeup that stands in the way of securing those environments.[1]

Is heritable the same as inherited? Is what is heritable always unchangeable?

Is to say that a trait is "heritable" the same as to say that it is "inherited", i.e., that the genes bequeathed to us by our parents contribute to its *etiology* in some way? Mills et al., who have computed the heritability of insulin secretion, seem to think so, as it appears from their assertion that high "heritability estimates of first- and late-phase insulin secretion (0.55 and 0. 58, respectively) underline the importance of inherited determinants of insulin secretion", which in turn is recognized as "a critical determinant of […] diabetes risk" (Mills & al. 2004, 737).

The question of what it is that heritability measures is a philosophical minefield that has filled pages describing endless wars between those who believe it

[1] Recently, the WHO Commission on the Social Determinants of Health concluded that health inequalities and poor health generally are caused by "unequal distribution of power, income, goods, and services, globally and nationally, the consequent unfairness in the immediate, visible circumstances of people's lives…not in any sense a 'natural' phenomenon but…the result of a toxic combination of poor social policies…unfair economic arrangements, and bad politics" (Commission on the Social Determinants of Health, 2008, 1). Elsewhere I have made a similar argument with respect to variations in the biological (albeit not genetic) predisposition to diabetes observed among different social groups (Chaufan, 2008). Close to two hundred years ago, Friedrich Engels made a similar, albeit far more forceful, argument concerning the poor health of the English working class (Engels, [1845] 1968).

illuminates the causal contribution of genes to traits, i.e., the nature-nurture question (Plomin & Asbury, 2005; Sesardic, 2005), and those who argue that applied to humans, I can only legitimize, overtly or covertly, eugenic social policies, yet it is useless to the enterprise of understanding functional relationships between genotypes and phenotypes (Joseph, 2006; Lewontin, 1974). And as I have shown, both friends and foes agree that heritability is the proportion of total phenotypic variance accounted for by genetic variance. Yet they disagree about whether this measurement quantifies *inheritance*.

But from Lush's widely accepted concept of heritability as a ratio of variances, it follows that it is perfectly possible, under certain environments, for a completely "environmental" trait to have a heritability of 1 (or 100%), or for a completely inherited trait to have a heritability of zero. For instance, in a society where eligibility for government office were reserved exclusively to men, the heritability of "being eligible for government office", arguably an "environmental" trait, would be 1 (or 100%), because if one divided the population between Group 1 (those with 0% chance of being eligible) and Group 2 (those with greater than a 0% chance), all one would need to make an accurate prediction would be to know whether an individual possessed an XX pair of sex chromosomes or an XY pair (Lerner, 1995). Put otherwise, the heritability of "being eligible for office" would compute all the phenotypic variability as explained (statistically) by genetic variability.

Conversely, a fully inherited trait such as having five fingers, which clearly does not vary with variations in nutritional states, childhood diseases, sun exposure, cultural practices, place of birth, and so forth, and is certainly caused by our human genome *somehow*, can have a heritability of zero if measured in a population in which, for instance, some individuals worked with machines that could sever their fingers and some did not. Generally, none of the variation we might find *in the trait in that population* would be caused by genetic differences but by environmental ones, unless one postulated gene variants that "predisposed" certain individuals to work with such machines. These extreme examples show that it would be incorrect to assume that estimates of heritability indicate the importance (or lack thereof) of genetic inheritance to a trait.

Moreover, let us note that if one ignored the existence of laws reserving government positions to men, or the relationship between number of fingers and certain work environments, plausible explanations for the observed phenotypic differences could indeed be hypothetical gene variants "influencing" eligibility for government office or number of fingers.

Let us further note that one needn't even ignore the influence of environmental factors to *inflate* heritability estimates: one could, as some authors have done, claim that the environments that lead to phenotypic differences are *actively selected* by the *genetically-driven* behaviors of *subjects themselves*, rather than *imposed* by others (Sesardic, 2003). Hence the *interaction* between an assumed genetically-driven behavior, for instance, a "propensity" to seek government positions, with the relevant environment, in this case, localities ruled by certain laws, ends up in the numerator, increasing the proportion of total phenotypic variance, i.e., holding a government position, explained, statistically, by genetic variance, thus "confirming" the "heritability" of the trait "eligibility for government office" and the "importance" of "genetic influences" to it.

The reasoning may raise a few eyebrows if applied to this extreme example. And yet this is precisely what Plomin and Asbury do when they propose that while parenting styles affect children's behaviors, it is in reality children's *genetically-driven behaviors* that *cause* parents to treat them in particular ways (2005), even as, oddly enough, parents' behaviors are assumed to display a remarkable phenotypic plasticity,

i.e., independence from *their own genes*, and readiness to respond to their children's genetically-caused behaviors (Joseph, 2004).

Thus what critics call *twins-create-their-own-environment theory*, no more than pseudoscience (Joseph, 2004), defenders contend is a reflection of the "nature of nurture", which explains how parenting styles, presumably only in appearance an environmental factor, may *confirm* the *influence* of children's genes on their own behaviors (via parental responses to these behaviors), thus showing that children's behaviors are inherited, to a great extent (Plomin & Asbury, (2005).

Heritability estimates are also often held as a measure of a condition's unchangeability, as Katoh et al. imply when they conclude that "the strong observed input from environmental factors" to diabetes, as measured by *environmental* variance (calculated by subtracting genetic variance from total phenotypic variance), "justifies strategies that address the importance of lifestyle changes" in diabetes prevention (2646). Yet if this were the case, inborn errors of metabolism such as phenylketonuria (PKU), which in the past was 100% heritable, would be forever untreatable other than through gene therapy (i.e. changing the defective gene), which is not the case (Lewontin, 2000)

The politics of science, numbers, and language

The arguments or evidence I have presented so far have limitations: they do not *conclusively* demonstrate that disease (or behavioral, or cognitive) genes do not exist – as logicians have taught us, it is very hard to prove a negative. Yet it is not unreasonable to assume that heritability estimates suggesting the existence of gene variants *explaining*, *influencing*, or *responsible for*, phenotypic differences, with little conceptual clarity about what exactly these terms might mean, are no more than a placeholder for our ignorance of the environmental, developmental, and stochastic processes influencing the traits of interest. And given the legitimacy of science, indeed of numbers, we can assume that these estimates pave the way for "supposedly morally neutral and objective experts" to make judgments not only about how the world is, but often about how it ought to be (Hirji, 2008; Zola, 1975).

In our day, the propagation of ambiguities and their legitimation as undisputed facts about the world are greatly enhanced by an uncritical media. For instance, *New York Times* health reporter Jane Brody has written that there is "nearly universal agreement" that 35% of the length of our lives is "determined" by our genes, a percentage over which we presumably have "little or no control" (Brody, 2008, F7). Of course Brody was merely reporting on the work of an expert in the science of longevity, Nir Barzilai, director of the Institute of Aging Research at the Albert Einstein College of Medicine in the Bronx, a prestigious institution, who has published on "human longevity-assurance genes" (Barzilai & Shuldiner, 2001, M83). And Brody must have reported correctly, as it appears from an interview by Claudia Dreifus, reporter at the same newspaper, to the scientist, in which he described his genetic endowment as "good for medicine, but mediocre for longevity", talked about his search of "longevity genes", and asserted that his group had found at least one such gene which "explain[ed] 18 percent of the longevity" (Dreifus, 2004, F5).

Setting aside that terms such as *explain* -- or *account for*, or *significance* -- may mean very different things to statisticians that they do to ordinary readers, and setting aside whether or not there truly exists any "universal agreement" about the percentage of longevity "explained" by genes – whatever this may mean -- it is remarkable that neither Brody nor Dreifus ever wonder just what these numbers might mean *when applied to any particular reader*. And most likely, many will walk away believing that there is a certain "percentage" of their own longevity,

large or small, "fixed" by their genes, over which they have "little or no control".

But, the skeptical reader might argue, what about environments that may help prevent or treat diabetes? Could heritability estimates not contribute *at least* to identifying them better? And is this not what Barzilai suggests when he asserts that his research might contribute to better indentify "environmental interventions to give [his parents], and perhaps, [himself], a long life", given their alleged lack of "longevity genes"? (Dreifus, 2004, F5).

But the problem with this assertion is that even if were possible to accurately compute the heritability of the vast majority of health conditions that most individuals are worried about, say, diabetes, with a view to eventually isolate diabetes genes, hence *indirectly* identify in which environments diabetes is *less* heritable (which is presumably what health researchers are interested in), there is overwhelming evidence *already* about which are those environments: at a minimum, proper perinatal nutrition and medical care, reasonable access to healthy lifestyles over the life course, and access to timely and quality medical care over the life course as well, all of them matters of economic, social and public health policies. Indeed, it would take an unusual optimism to believe that further measurements of heritability will contribute to promote those policies.

So what, if anything, illuminates the nature-nurture question? It is the concept of reaction norm, or, as geneticist Massimo Pigliucci has called it, *developmental reaction norm* (Pigliucci & Schlichting, 2006), a function of the relation among genotypes, environments, and phenotypes, the "real object of study both for programmatic and theoretical purposes" (Lewontin 1974, 404), and the topic of another paper (Chaufan, 2007).

Conclusions

Recapitulating, in humans, the heritability of diabetes, and most likely of comparable complex phenotypes, cannot be accurately measured, for empirical and ethical reasons. And even if it could, heritability would still say nothing about *how much* a person's genetic background has contributed to her fasting glucose concentration, height, or intelligence. An analysis of variance is not an analysis of causes, and cannot help understand what *caused* a condition in an individual, nor can it *quantify* contributing causes. It is not even an approximation of the question of nature-nurture -- it is *irrelevant* to it.

As to *heritable* and *inherited*, these terms have different meanings, and the ordinary language use of both as interchangeable is largely responsible for the persisting belief that the weight of inheritance can be meaningfully quantified in individuals. This belief is often fostered by scientists themselves, and reproduced by an uncritical media.

Now if, as I have tried to show, there is little *point* in calculating the heritability of complex human phenotypes, why, the reader might wonder, researchers *persist* in doing so and, based on it, they continue making the case that "genetics plays an important role in shaping political attitudes and ideologies" (Alford, Funk & al. 2005, 153), "antisocial behavior" (Brennan & Mednick, 1993), response to child abuse (Stokstad, 2002), intelligence (Plomin & Asbury, 2005) or diabetes (Katoh & al., 2005)? Why would critics of the concept be accused of "surprising lack of intellectual curiosity and analytical vacuity" (Sesardic 2005, 7) for insisting that the quantification of heritability needs to stop because it has nothing to offer to our understanding of human health and disease, and may even be harmful, by deviating public attention and moneys away from well-established social determinants?

Maybe hints to the answer lie in Barzilai's reply to Dreifus's question concerning how "longevity genes" might change the way medicine deals with aging. "[These findings] point to the possibility of a drug", replied the researcher. "There are several companies that are developing a drug to act on the gene I've

found and that is associated with longevity in my study" (Dreifus, 2004, F5). Or maybe they lie in the 400 million-dollar donation given by Eli and Edythe Broad to the Broad Institute of M.I.T. and Harvard, "the biggest gift so far", to "discover genetic links to major diseases […] which could lead to new ways to diagnose and prevent illness and develop medicines" (Strom, 2008, A16). Or in the 2.7 billion-dollar fund established by the U.S. Congress to sequence the human genome, with the goals, among others, of allowing scientists to "discover the genetic basis for health and the pathology of human disease […], implement an enhanced approach to preventive medicine, [and] determine which drugs work best for individuals, based on their genetic make-up" (National Human Genome Research Institute, 2008).

Maybe, as behavioral geneticist Douglas Wahlsten (1994) suggested, the persistence of the quantification of heritability is fueled by power struggles and by the peculiar interests of relevant social actors. Maybe this and similar attempts to partition nature and nurture say more about these power struggles and interests than about the origins of human biological, cognitive or behavioral variations.

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Claudia Chaufan *received her medical degree from the University of Buenos Aires and her doctorate in sociology with a philosophy notation from the University of California at Santa Cruz. Her intellectual interests include the political economy and social determinants of health, the sociology of social policies, the history, philosophy and sociology of the life sciences, and human rights and social justice. She has written about the diabetes epidemic and about health care systems, and given presentations on these topics in Argentina, in the United States, and in Europe. After a decade in clinical practice in Argentina, she is now an Assistant Professor of sociology and health policy at the University of California in San Francisco. She is active in the national movement for single-payer health care system reform.*

Resumen

Este artículo analiza el concepto de "heritabilidad" en su sentido técnico utilizado en investigaciones édicas (proporción de la variancia genética en relación a la variancia fenotípica total). Tomando la diabetes como una "enfermedad común" paradigmática, cuya heritabilidad se computa con frecuencia con el objeto de separar las contribuciones relativas de lo "innato" y lo "adquirido", este artículo tiene como objetivo ilustrar qué representa y qué no representa la heritabilidad y teorizar acerca de cuan aplicable es esta cuantificación a la práctica médica y a las políticas de salud. Este análisis es pertinente a los estudios de heritabilidad en enfermedades comparables a la diabetes o a fenotipos de similar complejidad. Este artículo concluye que tanto en diabetes como en fenotipos de complejidad similar la medida "heritabilidad" es incapaz de cuantificar y separar lo "innato" de lo "adquirido" en fenotipos humanos complejos, o de proveer información relevante a la práctica médicas o a políticas sanitarias. Un asunto interesante acerca de los estudios de heritabilidad, en diabetes y fenotipos similares, no es lo que contribuyen, o no contribuyen, al debate acerca de qué es innato y qué es adquirido, sino lo que estos revelan acerca de la naturaleza política y social de la practica médica y de las ciencias sociales.

Terminos claves: heritabilidad; innato-adquirido; diabetes tipo 2; determinantes sociales de la salud