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Reconstructing Dose: A Critique of McEniry's "Infant Mortality, Season of Birth, and the Health of Older Puerto Rican Adults"

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Some exposures that create biological differences among human populations act immediately or persist unchanged over time implying that researchers can simultaneously measure both dose and response. Others end well before their effects appear thereby requiring researchers to reconstruct dose *post hoc*. Studies of current and delayed effects complement each other because the failure to find a current exposure that explains how a population became biologically different from others should lead to a search for a prior exposure with a delayed effect.

Recent years have seen rapid growth in epidemiologic research attributing differences in the prevalence of disease across human populations to delayed effects. This growth could reflect both improved measurement of health disparities and a lack of success finding current exposures to explain them. We suspect, however, that the growth also reflects a belief in the public health community that demonstrating links between childhood exposures and adult disease will increase the impetus to improve maternal and child health.

McEniry's article in this issue of *Social Science and Medicine* (in press) provides an example of public health research into delayed effects by indirectly testing the hypothesis that poor nutrition and infection early in life increased heart disease and diabetes among older Puerto Ricans. As in many tests of delayed effects, McEniry had to reconstruct dose. She did so creatively but in a way sufficiently controversial that the editors felt publishing a critique of the approach would help readers assess the validity of her findings. We thank the editors for inviting us to provide that critique, and Professor McEniry for her patience during the review process.

We found McEniry's theory difficult to follow but we believe she argues the following. The hardness of cohorts *in utero* varies over time with the dose of environmental stressors on the population. A stressful environment that damages fetuses, and persists long enough to kill them in the first month of life, can "program" survivors in the cohort to yield high rates of heart disease and diabetes in adulthood. McEniry reports no such programming for diabetes but finds weak evidence for self-reported heart disease. She implies that, despite unknown external validity, her findings may encourage further work and inform attempts in the developing world to make environments less stressful for mothers and children.

We do not quarrel with attempts to make the world, developing or otherwise, less stressful. We doubt, however, that the findings reported in the article will add much impetus to public health research into delayed effects. Our skepticism arises not only from what we consider

questionable methods including ambiguous reconstruction of dose, but also from a failure to explore rival explanations of the empirical findings.

To start, we believe that skepticism legitimately arises from too terse a discussion of several limitations of the sample and data. McEniry says too little about the facts that, for example, 10% of births may not be recorded, many of the outcome variables come from self report, and that she had to impute 14% of sample scores on a key variable (i.e., “grew up in countryside”). We would, moreover, have liked to know the exact response rate for the interview.

A more serious threat to the validity of the analyses, however, arises from faulty classification rules. McEniry would have readers attribute a previously reported association between birth at the end of the harvest season and better adult health to “timing of nutritional insults during late gestation.” But her use of six-month birth groups as a proxy for *in utero* exposure to poor nutrition and infectious disease creates an “exposed” population with highly variable experiences during gestation and early life. She classifies infants born from July through December as exposed despite the fact that those born in July would have experienced a very different exposure from those born in December. A July birth implies an unexposed third trimester of gestation and an exposed first month of life, whereas a December birth implies the opposite (i.e., exposed third trimester and unexposed first month of life). This imprecise measurement belies the author’s statements regarding the importance of the timing of insults during gestation.

Another impediment to accepting McEniry’s results arises from her reconstruction of dose. As noted at the outset, studies of delayed effects typically succeed or fail to the degree that they can compellingly reconstruct dose *post hoc*. Doing so often requires surrogate indicators for exposure. McEniry chose infant mortality in each study participant’s *municipio* and year of birth as a surrogate. She cites Table 1 as evidence that the proportion of infant mortality attributable to neonatal mortality declines as the infant mortality rate increases. She infers that birth cohorts with low infant mortality rates had high neonatal mortality rates due, presumably, to damage *in utero* caused by stressors on the population. For this to be true, maternal exposure to environmental stressors during pregnancy would have to lead to increased *rates* of neonatal mortality not an increased ratio of neonatal to post-neonatal mortality. In Table 1, the neonatal mortality rate does not increase with lower infant mortality rates (in fact, it decreases). Post-neonatal mortality rates simply decrease faster over time than the neonatal mortality rate, likely reflecting improvements in public health and medical intervention that reduce post-neonatal more effectively than neonatal mortality. Put differently, McEniry cannot use low infant mortality rates as compelling proxies for high neonatal mortality rates (as appears to be assumed in the Endnote) or for *in utero* exposures.

We cannot obtain data that would allow us to estimate whether cohort neonatal and infant mortality rates correlated inversely, as McEniry argues, in the populations she studied. We, however, can estimate that relationship for 7.8 million California births to determine if more recent data support her argument. We computed neonatal and infant mortality rates for males and females for monthly birth cohorts born from January, 1989 through December,

2003. We then estimated the correlation between the neonatal and infant mortality rates using the raw sex specific rates, the detrended rates, and the rates with all autocorrelation removed. The latter two transformations test the notion that cohorts with rates higher or lower than expected (i.e., from trend or from any autocorrelation) would exhibit McEniry's inverse association. The associations between the neonatal and infant mortality rates for the series were positive (i.e., ranged from .71 to .88) with high levels of statistical significance. Although our point estimates may not describe Puerto Rico in the first half of the twentieth century, we doubt that the underlying biology of gestation and mortality has changed so fundamentally that the direction of association has reversed.

Given the above threats to the validity of McEniry's inferences regarding both season of birth and infant mortality rate, we caution readers against inferring meaning from McEniry's heart disease results. But other reviewers, perhaps wiser than we, concluded that the problems should not preclude publication of McEniry's inference that exposure to poor nutrition and perhaps other stressors in utero (measured by birth in the second half of the year) causes later life heart disease in birth cohorts with high rates of neonatal mortality (measured by birth in a year and place with low infant mortality). Accepting, for the sake of argument, that McEniry's variables measure phenomena as intended, we suggest that the discovered patterns could result from circumstances very different from those she posited. McEniry's inference regarding heart disease comes from an apparent interaction she describes as follows.

Overall models to test for interactions between season of birth and IMR group showed no significant effects for season of birth (OR 1.12, SE 0.20), but marginal effects for low/high IMR groups (OR 0.64, SE 0.14) and the interaction between the two (OR 1.87, SE 0.55). Estimation by the two IMR groups showed that the (1) effects of exposure (lean) period are significant and stronger for the Lower IMR group (Models 2a) and become insignificant for the Higher IMR group (Models 2b).

We believe that the literature describing early life selection across species offers a parsimonious explanation of McEniry's interaction. That literature suggests that natural selection has conserved mechanisms that in many species, including humans, end the development of individuals least likely to reproduce in stressful environments (Stearns, 1987). This selection occurs as early in development as the conserved mechanisms can assess the potential to reproduce. The first year of life presents much opportunity for selection in humans given that infant mortality exceeds the death rate for any other year before and through reproductive age.

McEniry argues, as described above, that low infant mortality in a given year implies that high doses of environmental stressors caused "endogenous" vulnerability *in utero* and attendant high neonatal death rates. Low infant mortality could, however, just as well mean that the year presented relatively mild stressors to mothers and neonates causing adults born in that year to include a relatively high fraction of individuals who would have died in infancy in birth years with less benign environments. The relative vulnerability of these cohorts could manifest itself in relatively high rates of heart disease later in life.

But why, then, the “interaction” in which only cohorts born in the second half of years with low infant mortality appear at risk of late life morbidity? Infants born in the second half of any year experience more of the environmental conditions peculiar to that year than those born in the first half. Any measure of annual conditions will therefore better characterize the perinatal exposures of infants born from July through December than those born from January through June. Any association McEniry found should appear stronger for cohorts born in the second than first half of the year thereby inducing an artifactual “interaction” effect.

Our interpretation of McEniry’s findings may not strike readers as any more satisfying than hers. But reduced selection, as indicated by low infant mortality, predicts later life morbidity without requiring the counter intuitive and unsubstantiated assumption that low infant mortality rates imply high neonatal mortality rates.

We would not argue that developing countries reduce adult heart disease by reducing shelter afforded women and children. But arguing that poor countries should make greater investments in such shelter in order to decrease heart disease in the elderly implies a level of empirical confidence beyond that provided by McEniry’s analyses of delayed effects. Such an argument also implies shifting scarce resources from other uses, water systems for example, that may have current or delayed salutary effects.

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