

NBER WORKING PAPER SERIES

PRIMATE EVIDENCE ON THE LATE HEALTH EFFECTS OF EARLY LIFE ADVERSITY

Gabriella Conti
Christopher Hansman
James J. Heckman
Matthew F. X. Novak
Angela Ruggiero
Stephen J. Suomi

Working Paper 18002
<http://www.nber.org/papers/w18002>

NATIONAL BUREAU OF ECONOMIC RESEARCH
1050 Massachusetts Avenue
Cambridge, MA 02138
April 2012

This work was supported in part by the American Bar Foundation, the JB & MK Pritzker Family Foundation, Susan Thompson Buffett Foundation, NICHD R37-HD065072, NIA R01-AG034679, a project with the Becker Friedman Institute for Research and Economics funded by the Institute for New Economic Thinking (INET), and an anonymous funder. The views expressed in this paper are those of the authors and not necessarily those of the funders or commentators mentioned here. We are very grateful to Ruth A. Woodward (D.V.M.) for providing us with the medical records, and to Ernest B. Davis for providing us with the behavioral observations. We also thank Meiping Sun for her help in the data collection process in the first stage of this process. The views expressed herein are those of the authors and do not necessarily reflect the views of the National Bureau of Economic Research.

NBER working papers are circulated for discussion and comment purposes. They have not been peer-reviewed or been subject to the review by the NBER Board of Directors that accompanies official NBER publications.

© 2012 by Gabriella Conti, Christopher Hansman, James J. Heckman, Matthew F. X. Novak, Angela Ruggiero, and Stephen J. Suomi. All rights reserved. Short sections of text, not to exceed two paragraphs, may be quoted without explicit permission provided that full credit, including © notice, is given to the source.

Primate Evidence on the Late Health Effects of Early Life Adversity
Gabriella Conti, Christopher Hansman, James J. Heckman, Matthew F. X. Novak, Angela Ruggiero, and Stephen J. Suomi
NBER Working Paper No. 18002
April 2012
JEL No. I12,J13

ABSTRACT

This paper exploits a unique ongoing experiment to analyze the effects of early rearing conditions on physical and mental health in a sample of rhesus monkeys (*Macaca mulatta*). We analyze the health records of 231 monkeys which were randomly allocated at birth across three rearing conditions: Mother Rearing, Peer Rearing, and Surrogate Peer Rearing. We show that the lack of a secure attachment relationship in the early years engendered by adverse rearing conditions has detrimental long-term effects on health which are not compensated by a normal social environment later in life.

Gabriella Conti
Harris School of Public Policy
University of Chicago
1155 East 60th Street
Chicago, IL 60637
and NBER
gconti@uchicago.edu

Matthew F. X. Novak
Department of Psychology
Central Oregon Community College
Modoc 212
2600 N.W. College Way
Bend OR 97701
mnovak@cocc.edu

Christopher Hansman
Department of Economics
Columbia University
1022 International Affairs
420 West 118th Street
New York, NY 10027
cjh2182@columbia.edu

Angela Ruggiero
NICHD
Section on Comparative Behavioral Genetics
Elmer School Rd Room 205
Poolesville MD 20837
ar327u@nih.gov

James J. Heckman
Department of Economics
The University of Chicago
1126 E. 59th Street
Chicago, IL 60637
and University College Dublin and IZA
and also NBER
jjh@uchicago.edu

Stephen J. Suomi
NICHD
Section on Comparative Behavioral Genetics
Elmer School Rd Room 205
Poolesville MD 20837
suomis@mail.nih.gov

An online appendix is available at:
<http://www.nber.org/data-appendix/w18002>

The importance of the early years in affecting a variety of aspects of later life, including health, through the “biological embedding” of early experiences is now widely recognized (see Essex et al., 2011; Fox et al., 2010; Hertzman and Boyce, 2010). Some of the most compelling evidence on the consequences of early maternal and social deprivation comes from children raised in the adverse settings of Romanian orphanages of the 1980s and 90s. Lasting physiological and mental effects have been striking there: the most recent findings (Rutter, 2010) show a high degree of persistence until fifteen years of age of quasi-autism, disinhibited attachment, inattention/overactivity, and cognitive impairment.¹ Another environment in which children have been deprived of normal maternal relationships is that of the Israeli Kibbutz, where they were raised collectively, living among peers with the community providing for material needs from a young age. Lieblich (2010) provides a recent overview of the research on kibbutzim, concluding that children raised in these environments do not tend to strive for excellence, that the development of personal identity is hampered, and that the quality of their relationships when adults is diminished. However, they do not show emotional problems typically found in other institutionally raised children.

Apart from these atypical environments, the literature abounds with observational evidence on children who have been abused or neglected, or who have somehow not formed secure attachment relationships to their primary caregivers, and have subsequently displayed maladaptive patterns of development (see, for example, Cicchetti and Toth 1995; Dube et al. 2003; Nunes et al. 2010). Manipulating environments experimentally, however, is challenging with data on humans,² and for decades researchers have employed non-human primate models to explore the behavioral and physiological effects of early maternal and social deprivation. While the devastating social consequences of early isolation have been recognized since Harlow’s work in the 1950s and 1960s (e.g., Harlow and Zimmermann, 1959), more recent work has begun to uncover the impact of adverse rearing experiences on more direct physiological measures, including hormonal changes, brain function and gene expression. For example, Dettmer et al. 2012 characterize the relationships between rearing conditions, measures of anxiety, and hair cortisol concentrations. While significant differences across rearing conditions with respect to both hair cortisol and anxiety-related behaviors are present, they largely disappear by age two. Alternatively, Feng et al. (2011) show that the altered cortisol response to acute stressors in peer-reared monkeys is not reversed after 1.5 years of normal life. Additionally, Spinelli et al. (2009) find that peer-reared monkeys display enlargement in stress-sensitive brain regions when compared with mother-reared monkeys, and Jackowski et al. (2011) document that male bonnet monkeys subject to early stress show effects in brain development in multiple regions involved in emotion processing, such as the corpus callosum and the hippocampus. However,

¹In addition, in the absence of subnutrition, children whose institutional deprivation lasted beyond the age of 6 months had a major constraint in head growth. Orphans have been studied in a number of contexts, see Bakermans-Kranenburg et al. (2008) for a meta analysis of existing studies.

²See Heckman et al. (2010) and Schweinhart et al. (2005) for a recent exception.

despite the broad range of studies focusing on behavioral changes and physiological markers, relatively few studies have analyzed the health consequences of adverse early rearing conditions, focusing either on growth, reproduction and survival (see, for example Sackett et al., 2002), or on cell-mediated immune response (like Coe et al. 1989 and Gordon et al. 1992). In a recent review, Schapiro (2002) summarizes these studies concluding that animate rather than inanimate enrichment (i.e. social housing rather than feeding enhancements) is more effective in ameliorating the negative health consequences of adverse early conditions.

This paper contributes to the literature by exploiting experimental data on a sample of rhesus monkeys (*macaca mulatta*),³ subject to a randomized early rearing protocol to show evidence that the lack of a secure attachment relationship early in life has detrimental consequences on physical and mental health later in life. Furthermore, we show evidence that these effects differ by gender, and stretch beyond the first year, suggesting that the consequences of early adversity “get under the skin”, and are not compensated for by living in a normal social environment later in life.

1 Data

Our data set was obtained from records collected up to January 2010 on 231 Rhesus Macaques, born between 2002 and 2007 and raised in the Laboratory of Comparative Ethology, NICHD primate facilities at the National Institute of Health Animal Center as part of an ongoing randomized experiment. At birth all subjects were randomized into one of three rearing conditions: Mother Reared (MR), Peer Reared (PR), and Surrogate Peer Reared (SPR or Surrogate Reared). MR monkeys remained with their biological mothers from birth and were raised in large cages with other monkeys, while both PR and SPR were taken from their mothers and individually raised in a nursery until the 37th day of life.⁴ On the 37th day, PR monkeys were placed in groups of 4 with the 3 monkeys closest in age. Monkeys in the same group spent 24 hours together in a cage and were removed only for testing. SPR monkeys spent 22 hours a day alone in a cage with a “surrogate” mother (effectively a terry-cloth-covered hot water bottle hanging from the top of the cage), and were placed with a peer group of 3 other SPR monkeys in a “play” cage that provided the opportunity for unlimited social interaction for the remaining two hours each day. Between 6 months and 1 year, all monkeys born in the same year were put together

³While they are not our closest genetic relatives among nonhuman primates (they share about 95% of human genes, while chimpanzees and bonobos share 98-99%), they are like humans and unlike virtually every other species of nonhuman primates, in their versatility and ability to adjust to and survive in almost any climate in the world. For more on the closeness between humans and macaques, see Maestriperieri (2007).

⁴While all Nursery Reared (NR) monkeys are not breastfed, formula-feeding cannot be considered the sole reason for our findings, as we observe differences between types of NR monkeys (PR vs. SPR).

in a single mixed social group.⁵ MR monkeys constitute just over 50% of our sample, while PR and SPR monkeys make up just under 25% each (122, 57 and 52, respectively); a slight majority of our sample is male (126), and just under a quarter of them were firstborn (56) (see Table A1 in the Web Appendix for summary statistics).

The five outcomes analyzed in this paper are based on records from two sources: physical examinations and behavioral observations. Both were first performed at birth and continued throughout the lifecycle.⁶ Physical exams were performed 4 times a year by the facility veterinarians using a standardized worksheet. Items on this worksheet included physiological measures such as weight, a checklist for problems in various main bodily regions, and a space for descriptions of particular health issues not explicitly listed in a pre-specified category. In our analysis, we examine 3 outcomes culled from these worksheets: a continuous measure of weight, and binary indicators for both health issues arising from wounds (“Wound”), and health issues not due to external bodily harm (“Illness”). The category “illness” is constructed by including health issues recorded in two different parts of the primate physical health worksheet: problems in various main bodily regions (EENT,⁷ Mouth/Head, Chest, Abdomen, Urogenital), and issues recorded in the “Other” section (the main categories here being diarrhea, rash and hernia). The additional outcome measures that we analyzed are binary indicators for the occurrence of any stereotypic behavior (“Stereotypy”)⁸ and the presence of hair loss (“Alopecia”), obtained from 5-minute focal points behavioral observations, performed biannually by a skilled technician from the NICHD Research Animal Management Branch. For each dichotomous outcome reported, we construct two measures: one indicator of overall *prevalence*, which indicates whether the animal experienced the condition at any point during the period for which we have data available; and one indicator of *frequency*, which indicates the proportion of visits/observations in which the condition was recorded. Illness and stereotypy have approximately the same frequency (18% and 21%, respectively), while alopecia is recorded, on average, in 14% of the observations, and wounds are recorded in 9% of the visits. In terms of overall prevalence, this amounts to 74% for illness, 48% for wound and 46% for both stereotypy and alopecia (i.e. 172, 111, 106 and 107 monkeys have been recorded showing that particular condition at least once during the full period of observation, respectively; see Table A1 in the Web Appendix). When breaking down the category “illness” into its various components, we notice that 171 monkeys experience an illness due to problems in main bodily regions (henceforth “main illness”) at least once during the period for which we have data available, with an average frequency of 17%, and that 71 monkeys

⁵Given that the average life of a monkey is 25 years in captivity, the period spent in treatment can be thought of as the critical 0-3 years in humans.

⁶Both the examinations and the observations are carried out uniformly across the rearing groups in our sample.

⁷Ears, Eyes, Nose and Throat.

⁸The full list of stereotypies observed includes: digit sucking (the most frequent behavior), pacing, head tossing, self-grasping, saluting, spinning, rocking, circling, and swinging.

experience an illness due to other problems (henceforth “other” illness), with an average frequency of 5%. Among the “other” illnesses, the numbers are fairly equally split between diarrhea and non-diarrhea-related conditions. A further breakdown shows that problems related to mouth and head are the most common pathologies in the “main” category, and that rashes are most common after diarrhea in the “other” category.

2 Results

We present three main results on the later-life health effects of adverse early rearing conditions, reported in Tables 1-4. We state and discuss each of them in turn:

- (1) *Physical Health: Surrogate Peer Reared male monkeys exhibit a statistically significantly higher probability of developing illnesses, both in terms of prevalence ($p = 0.025$) and in terms of frequency ($p = 0.004$).*

Panel (a) in Figure 1 clearly shows that the predicted frequency of illness for a SPR monkey is 0.274, almost twice as much as for a MR monkey (0.154).⁹ The effect on prevalence is much more dramatic, with almost all the SPR male monkeys having experienced an illness at least once during the observation period. The adverse effects of surrogate peer rearing survive the multiple hypothesis testing correction, as can be seen in the last column of Panel A in Table 1.

These results provide evidence of a causal link between early maternal and social deprivation and later life illness;¹⁰ additionally, we supplement our analysis with additional data on cortisol, ACTH and 5-HIAA,¹¹ collected while the monkeys are still in their respective treatment conditions (i.e., before one year of age). We show that, consistent with Dettmer et al. (2012), our results are in line with the large body of observational evidence on humans on the role played by stress as a mediating factor between childhood adversity and later life disease (see Gunnar and Fisher, 2006; McEwen, 1998; Repetti et al., 2002): we find higher cortisol levels among SPR male monkeys, and deficits in both ACTH (AdrenoCortitropic Hormone, as in Clarke et al. 1998) and in serotonin metabolism, as they have lower concentrations of 5-HIAA (the primary central serotonin metabolite), which is linked to aggression and antisocial behavior in

⁹The value for SPR is obtained summing the frequencies in the “Control mean” and “Condit.” columns in Table 1.

¹⁰Our findings are consistent with those of Lewis et al. (2000), who note lifelong differences in cellular immune functioning, and higher mortality rates, amongst monkeys reared in isolation (with a protocol similar to the Surrogate Peer Reared).

¹¹Blood (assayed for ACTH and cortisol) and cerebrospinal fluid (CSF, assayed for concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid 5-HIAA with gas chromatography-mass spectrometry) were collected in days 60, 90, 120 and 150, in the first five months of life of the monkeys, up until 2005 (so they are only available for a subsample). Since they were collected while the monkeys were still in their separate rearing conditions, it is notable that visible health effects outlast this initial period.

both humans and primates (see Higley et al., 1996; Moore et al., 2002). Notice that all these effects survive the multiple hypothesis testing corrections (see Panel A in Table A4 in the Web Appendix).

When breaking down the “illness” category into its various components (see Table 2),¹² we notice that, while the adverse health effects of surrogate peer rearing seem pervasive,¹³ only the effects on diarrhea survive the multiple hypothesis testing correction. Due to the importance of diarrhea (which could be due to bacterial agents (*campylobacter* and *shigella* being the most common) or be chronic in nature) in explaining the noted effects, we exploit additional information on medicines taken and blood test results for a small subsample of 34 monkeys to gain more insights into this condition. The medicines most commonly administered were erythromycin,¹⁴ metronidazole,¹⁵ baytril¹⁶ and imodium¹⁷. Further the, analysis of the blood test results (reported in Table A3 in the Web Appendix) reveal that male monkeys affected by diarrhea show abnormally lower values of sodium and potassium (as consequence of dehydration), abnormally higher values of blood urea nitrogen, and higher values of hematocrit and glucose (these values were much less altered for diarrhea-affected females).

(2) *Mental Health: Nursery Reared (both Peer and Surrogate Peer Reared) monkeys of both genders exhibit a significantly higher probability of developing stereotypies, both in terms of prevalence and in terms of frequency ($p = 0.000$ for both genders and rearing groups).*

While the development of stereotypic behavior in response to adverse rearing conditions has been documented since the 1960s (Champoux et al., 1991; Harlow and Harlow, 1962; Suomi et al., 1974), recent research on humans gives a renewed importance to understanding this relationship. Bos et al. (2010) examine the connection between early institutionalization, foster care, and stereotypies in a cohort of Romanian children with a history of institutional care. Their results establish evidence of an association between institutionalization and stereotypic behavior, as well as between stereotypic behavior and cognitive and language deficits. They demonstrate the potential for remediation through foster care. Such work emphasizes the importance of stereotypies in humans, given the association between stereotypic behavior and both autism and intellectual disabilities (Wolf, as cited in Bos et al., 2010). In light of these findings, our results serve not only to highlight the parallels between nursery rearing in monkeys and institutionalization in human infants, but also demonstrate the power of adverse early experience to produce behavioral abnormalities which are, at the very least, markers of deeper developmental deficits. It should also

¹²Full results are presented in Tables A2 and A3 in the Web Appendix.

¹³Many outcomes are statistically significant when performing single hypothesis testing.

¹⁴Used in the treatment of diarrhea by *campylobacter*.

¹⁵Used in the treatment of diarrhea by *clostridium difficile*.

¹⁶Used in the treatment of diarrhea by *shigella*.

¹⁷Used in the treatment of diarrhea due to IBS

be noted that in males, surrogate peer rearing produces significantly higher frequency of stereotypies, as compared to peer rearing (see Panel (b) of Figure 1), while in females the two rearing statuses are not significantly differently affected (see Panel (c) of Figure 1).¹⁸

(3) *Peer Reared female monkeys exhibit a significantly higher probability of being wounded ($p = 0.046$) and of experiencing alopecia, both in terms of prevalence ($p = 0.024$) and in terms of frequency ($p = 0.017$), and have a significantly higher weight than their Mother Reared or Surrogate Peer Reared counterparts ($p = 0.043$).*

Hence, as displayed in Panels (c)-(d) of Figure 1, it appears that female monkeys raised with males in mixed-gender groups develop patterns of behavior which are convergent with those of males. Again, we supplement our analysis with additional data collected while the monkeys were still in their separate rearing conditions, to investigate the early behavioral origins of these later life differences.¹⁹ We find that PR females display higher levels of aggressivity in comparison to MR females (evidence presented in Table A5 in the Web Appendix), suggesting that alopecia might be partly due to hair pulling by others,²⁰ and that, contrary to SPR females, they did not show self-grooming (which includes self-scratching or biting) behavior,²¹ suggesting that the wounds recorded during the physical exam are likely not due to self-harm.²² A similar reduction in the typical sexual dimorphism is observed with respect to weight: the weight of peer reared animals of both sexes effectively converges (the mean difference between the weight of male and female PR monkeys in our sample is a mere 12 grams, which is not statistically significantly different from zero, see Panels (e)-(f) of Figure 1²³). We interpret this convergence pattern as the result of the influence of the early social rearing environment (peer groups are of mixed gender) on the expression of behavioral sex differences.²⁴ We observe converging patterns for both male and female monkeys, and for neither of them do we find statistically significant evidence of a stress-related response (no statistically

¹⁸Feng et al. (2011) also recently showed that peer-reared monkeys have an increase in stereotypical behaviors as compared to mother-reared monkeys. However, they do not carry out their analysis by gender.

¹⁹Given the external nature of wounds and alopecia, we examined whether behavioral differences across monkeys allocated to different rearing conditions, as opposed to physiological changes, could account for this effect.

²⁰Novak and Meyer (2009) notice that it can be due to a variety of factors, including nutritional imbalances and hair pulling by others.

²¹Aggressive and self-grooming behavior were recorded twice per week, in the first 36 weeks of life of the monkeys.

²²Lutz et al. (2007) also report that self-biting is more common among SPR than among MR or PR monkeys. Aggressive behavior and self-grooming was recorded in the first 30 weeks of life of the monkeys, when they were still in their separate rearing conditions. It is notable that visible differences manifest so early and translate into later behavioral differences.

²³We do observe, instead, statistically significant gender differences between MR (459 grams) and SPR monkeys (943 grams).

²⁴See Wallen (1996) for a review of the role of nature and nurture on the development of sexually dimorphic behavior in rhesus monkeys.

significant difference in both cortisol levels, ACTH and 5-HIAA concentration in the female PR monkeys as compared to the MR ones, as shown in Panel D of Table A4 in the Web Appendix).²⁵ Importantly, while gender differences in the effects of early-life experiences on behavior have already been reported in the literature (see among the earlier studies Sackett 1970 and Sackett 1972, who show that males are much more affected by early deprivation than females), to the best of our knowledge our study is the first time to document differential response by sex with respect to health outcomes.

3 Methods

The strength of our research design stems from the experimental manipulation of the early environment, as the monkeys are randomly allocated at birth across different rearing conditions. In this way, we exploit the major benefit of randomization, which is avoiding the problem of selection bias, i.e. ensuring that $(Y_0, Y_1) \perp\!\!\!\perp D$, where D is the treatment assignment indicator (where monkeys can be assigned to either the PR or to the SPR condition), “ $\perp\!\!\!\perp$ ” stands for statistical independence, and (Y_0, Y_1) are vectors of potential outcomes for treated and control units.²⁶ However, the benefits of randomization in terms of protection against bias from unknown potentially influential factors are lost when the allocation of participants to treatment and control units is compromised, i.e. when treatments and controls have imbalanced covariate distribution. In our case, this occurs for two reasons: there is imbalance of rearing statuses across cohorts,²⁷ and first borns are preferentially kept with mothers according to lab protocol. The assumption of independence between potential outcomes and treatment assignment has to be modified to read: $(Y_0, Y_1) \perp\!\!\!\perp D|X$, where X is year of birth and primiparousness. Since we have knowledge of the variables which determine assignment to treatment, we can match on them to account for departures from the randomization protocol.

Our aim is to test the null hypothesis of no effect of PR and SPR treatment

²⁵Another possible explanation for these findings would be related to the dynamics of social hierarchy after the transition from the respective rearing environments to the common social group, and its relation to weight gain (see Bastian et al., 2003): unfortunately, the current unavailability of social dominance data and of information on food consumption and on stress-related biomarkers after the end of the treatment prevents us to assess the plausibility of this explanation, so we defer the answer to this question to another occasion.

²⁶See Heckman (2005) for a thorough discussion of the scientific model of causality. The standard model of program evaluation describes the observed outcome for participant i , Y_i , by $Y_i = D_i Y_{i,1} + (1 - D_i) Y_{i,0}$, where $(Y_{i,0}, Y_{i,1})$ are potential outcomes corresponding to control and treatment status for participant i , respectively, and D_i is the assignment indicator: $D_i=1$ if treated, 0 otherwise. An evaluation problem occurs because either $Y_{i,0}$ or $Y_{i,1}$ is observed, but not both. Properly designed and implemented randomized experiments can eliminate this problem because they produce independence between $(Y_{i,0}, Y_{i,1})$ and D_i . Within this setup, we refer throughout in our analysis to “treatment” as the PR and SPR conditions, and to “control” as the MR condition.

²⁷Older cohorts are more likely to be SPR.

conditions on several later life outcomes, which can be formally stated as follows:

$$Y \perp\!\!\!\perp D_{PR}|X$$

and

$$Y \perp\!\!\!\perp D_{SPR}|X$$

where Y is the outcome vector, and $D = 0$ if MR, and $D = 1$ if PR or SPR, respectively. However, our small sample size calls into question the validity of applying classical tests based on large sample statistical theory. Hence, we use permutation-based inference as an alternative approach: we perform one-sided permutation tests²⁸, applying the Freedman-Lane procedure, and using as covariates year of birth and total time spent in the primate center, and restricting the permutation orbits within strata formed by being first or later born.²⁹ Additionally, as we consider several prevalence and frequency measures. To avoid the problems of multiple hypothesis testing and selecting singly “significant” results from a set of largely statistically insignificant outcomes, we control for multiple hypothesis testing using the stepdown procedure developed in Romano and Wolf (2005).³⁰

Importantly, throughout we only consider outcomes measured *after* the first year, when all monkeys have been placed into a common mixed social group, to study the long-term effects of adverse early rearing conditions. Additionally, we exploit supplementary data on intermediate phenotypes to try to understand the mechanisms – both physiological and behavioral – underlying the observed changes in later-life health outcomes, in order to dig deeper and go beyond the estimates of average treatment effects.³¹

²⁸We allowed for unequal variances across the groups.

²⁹This is the approach that was used in the evaluation of the Perry Preschool Program by Heckman et al. (2010). This involved testing a null hypothesis (i.e. the hypothesis that the experiment had no impact) using permutations of the data. Taking permutations of the data means randomly switching the treatment assignment of the monkeys between the MR, and the PR and SPR conditions, respectively. The null hypothesis of no treatment effect is equivalent to the statement that the distribution of the outcomes of the treatment and control groups are the same. We used 10,000 permutations throughout.

³⁰See Heckman et al. (2010) for a recent application. This method corrects for multiple hypothesis testing using the family-wise error rate (FWER), i.e. the probability of obtaining one or more false positives out of a set of hypotheses tests. Romano and Wolf (2005) have shown that this stepdown procedure exhibits strong FWER control, it is less conservative than traditional procedures, and obtains gain in power from accounting for statistical dependencies among the test statistics associated with each individual hypothesis. See the Methods section for details on the implementation of the procedures we adopt.

³¹While we base our analysis on a randomized experiment, we recognize the importance of understanding the mechanisms to accumulate useful knowledge – which can be used as basis for implementation of policies. Inferences of causality based on increasing understanding over time of underlying mechanisms at the basis of observed effects are central to the process of knowledge accumulation. The successive developments and extensions of the Henle-Koch postulates, and the corresponding changing guidelines for evaluating the causal role of an agent in infectious disease, following technical developments in microbiology, provide a clear example of the difficulties intrinsic to positing “sufficient” conditions for establishing causality (see Evans, 1976, 1991).

4 Conclusions

While the importance of the early years of life in affecting adult outcomes is now recognized, establishing the existence of a causal effect on health of early exposure to adversity can be a challenging task. In this paper, we exploit a unique ongoing experiment in a colony of rhesus monkeys to provide causal evidence of the health effects of early maternal and social deprivation. We show that the lack of a secure attachment relationship in the early years has detrimental consequences for both physical and mental health later in life, with long-lasting effects which vary by gender. The persistence of these effects after the end of the treatment emphasizes the need to intervene early in life to prevent long-term damage.

References

- Bakermans-Kranenburg, M., M. van Ijzendoorn, and F. Juffer (2008). Earlier is better: A meta-analysis of 70 years of intervention improving cognitive development in institutionalized children. *Monographs of the Society for Research in Child Development* 73(3), 279–293.
- Bastian, M., A. Sponberg, S. Suomi, and J. D. Higley (2003). Long-term effects of infant rearing condition on the acquisition of dominance rank in juvenile and adult rhesus macaques (*Macaca mulatta*). *Developmental Psychobiology* 42(1), 44–51.
- Bos, K. J., J. Zeanah, Charles H., A. T. Smyke, N. A. Fox, and I. Nelson, Charles A. (2010). Stereotypies in children with a history of early institutional care. *Archives of Pediatrics and Adolescent Medicine* 164(5), 406–411.
- Champoux, M., B. Metz, and S. Suomi (1991). Behavior of nursery/peer-reared and mother-reared rhesus monkeys from birth through 2 years of age. *Primates* 32, 509–514.
- Cicchetti, D. and S. Toth (1995). A developmental psychopathology perspective on child abuse and neglect. *Journal of the American Academy of Child and Adolescent Psychiatry* 34(5), 541–565.
- Clarke, A., G. W. Kraemer, and D. J. Kupfer (1998). Effects of rearing condition on hpa axis response to fluoxetine and desipramine treatment over repeated social separations in young rhesus monkeys. *Psychiatry Research* 79(2), 91–104.
- Coe, C. L., G. R. Lubach, W. B. Ershler, and R. G. Klopp (1989). Influence of early rearing on lymphocyte proliferation responses in juvenile rhesus monkeys. *Brain, Behavior, and Immunity* 3(1), 47–60.
- Dettmer, A., M. Novak, S. Suomi, and J. Meyer (2012). Physiological and behavioral adaptation to relocation stress in differentially reared rhesus monkeys: Hair cortisol as a biomarker for anxiety-related responses. *Psychoneuroendocrinology* 37(2), 191–199.
- Dube, S., V. Felitti, M. Dong, W. Giles, and R. Anda (2003). The impact of adverse childhood experiences on health problems: Evidence from four birth cohorts dating back to 1900. *Preventative Medicine* 37(3), 268–277.
- Essex, M., W. Boyce, C. Hertzman, L. Lam, J. Armstrong, S. Neumann, and M. Kobor (2011). Epigenetic vestiges of early developmental adversity: Childhood stress exposure and dna methylation in adolescence. *Child Development*. in press.
- Evans, A. S. (1976). Causation and disease: The Henle-Koch postulates revisited. *Yale Journal of Biology and Medicine* 49(2), 175–195.

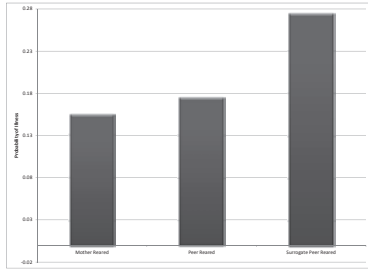
- Evans, A. S. (1991). Causation and disease: effect of technology on postulates of causation. *Yale Journal of Biology and Medicine* 64(5), 513-528.
- Feng, X., L. Wang, S. Yang, D. Qin, J. Wang, C. Li, L. Lv, Y. Ma, and C. Hu (2011). Maternal separation produces lasting changes in cortisol and behavior in rhesus monkeys. *Proceedings of the National Academy of Sciences* 108(34), 14312-14317.
- Fox, S., P. Levitt, and C. Nelson III (2010). How the timing and the quality of early experiences influence the development of brain architecture. *Child Development* 81(1), 28-40.
- Gordon, T., D. Gust, M. Wilson, A. Ahmed-Ansari, A. Brodie, and H. McClure (1992). Social separation and reunion affects immune system in juvenile rhesus monkeys. *Physiology and Behavior* 51(3), 467-472.
- Gunnar, M. R. and P. A. Fisher (2006). Bringing basic research on early experience and stress neurobiology to bear on preventive interventions for neglected and maltreated children. *Development and Psychopathology* 18(3), 651-677.
- Harlow, H. and R. Zimmermann (1959). Affectional responses in the infant monkey. *Science* 130(3373), 419-467.
- Harlow, H. F. and M. K. Harlow (1962). The effect of rearing conditions on behavior. *Bulletin of the Menninger Clinic* 26(5), 213-224.
- Heckman, J. J. (2005, August). The scientific model of causality. *Sociological Methodology* 35(1), 1-97.
- Heckman, J. J., S. H. Moon, R. Pinto, P. A. Savelyev, and A. Q. Yavitz (2010). Analyzing social experiments as implemented: A reexamination of the evidence from the HighScope Perry Preschool Program. *Quantitative Economics* 1(1), 1-46. First draft, September, 2006.
- Hertzman, C. and T. Boyce (2010). How experience gets under the skin to create gradients in developmental health. *Annual Review of Public Health* 31, 329-347.
- Higley, J. D., P. T. Mehlman, R. E. Poland, D. M. Taub, J. Vickers, S. J. Suomi, and M. Linnoila (1996). CSF testosterone and 5-HIAA correlate with different types of aggressive behaviors. *Biological Psychiatry* 40(11), 1067-1082.
- Jackowski, A., T. D. Perera, C. G. Abdallah, G. Garrido, C. Y. Tang, J. Martinez, S. J. Mathew, J. M. Gorman, L. A. Rosenblum, E. L. Smith, A. J. Dwork, D. C. Shungu, A. Kaffman, J. Gelernter, J. D. Coplan, and J. Kaufman (2011). Early-life stress, corpus callosum development, hippocampal volumetrics, and anxious behavior in male nonhuman primates. *Psychiatry Research: Neuroimaging* 192(1), 37-44.

- Lewis, M. H., J. P. Gluck, J. M. Petitto, L. L. Hensley, and H. Ozer (2000). Early social deprivation in nonhuman primates: long-term effects on survival and cell-mediated immunity. *Biological Psychiatry* 47(2), 119 – 126.
- Lieblich, A. (2010). A century of childhood, parenting, and family life in the kibbutz. *Journal of Israeli History* 29(1), 1–24.
- Lutz, C. K., E. B. Davis, A. M. Ruggiero, and S. J. Suomi (2007). Early predictors of self-biting in socially-housed rhesus macaques (*Macaca mulatta*). *American Journal of Primatology* 69(5), 584–590.
- Maestripieri, D. (2007). *Macchiavellian intelligence: how rhesus macaques and humans have conquered the world*. Chicago, IL: University Of Chicago Press.
- McEwen, B. S. (1998). Seminars in medicine of the beth israel deaconess medical center: Protective and damaging effects of stress mediators. *The New England Journal of Medicine* 338(3), 171–179.
- Moore, T. M., A. Scarpa, and A. Raine (2002). A meta-analysis of serotonin metabolite 5-HIAA and antisocial behavior. *Aggressive Behavior* 28(4), 299–316.
- Novak, M. A. and J. S. Meyer (2009). Alopecia: Possible causes and treatments, particularly in captive nonhuman primates. *Comp Med* 59(1), 1826.
- Nunes, S., M. Watanabe, H. Morimoto, R. Moriya, and E. Reiche (2010). The impact of childhood sexual abuse on activation of immunological and neuroendocrine response. *Aggression and Violent Behavior* 15(6), 440–445.
- Repetti, R. L., S. E. Taylor, and T. E. Seeman (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin* 128(2), 330–366.
- Romano, J. P. and M. Wolf (2005, March). Exact and approximate stepdown methods for multiple hypothesis testing. *Journal of the American Statistical Association* 100(469), 94–108.
- Rutter, M. (2010). Deprivation-specific psychological patterns: effects of institutional deprivation. *Monographs of the Society for Research in Child Development* 75(1), 1–242.
- Sackett, G. (1970). Innate mechanisms, rearing conditions, and a theory of early experiences effects in primates. In M. Jones (Ed.), *Miami Symposium on the prediction of behavior: Effects of early experience*. Miami: University of Miami Press.
- Sackett, G., G. Ruppenthal, and A. Davis (2002). Survival, growth, health, and reproduction following nursery rearing compared with mother rearing in pigtailed monkeys (*Macaca nemestrina*). *American Journal of Primatology* 56(3), 165–183.

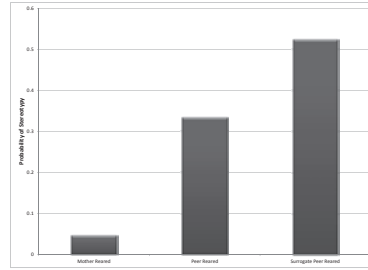
- Sackett, G. P. (1972). Exploratory behavior of rhesus monkeys as a function of rearing experiences and sex. *Developmental Psychology* 6(2), 260–270.
- Schapiro, S. J. (2002). Effects of social manipulations and environmental enrichment on behavior and cell-mediated immune responses in rhesus macaques. *Pharmacology Biochemistry and Behavior* 73(1), 271–278.
- Schweinhart, L. J., J. Montie, Z. Xiang, W. S. Barnett, C. R. Belfield, and M. Nores (2005). *Lifetime Effects: The High/Scope Perry Preschool Study Through Age 40*. Ypsilanti, MI: High/Scope Press.
- Spinelli, S., S. Chefer, S. Suomi, J. D. Higley, C. Barr, and E. Stein (2009). Early-life stress induces long-term morphologic changes in primate brain. *Archives of General Psychiatry* 66(6), 658–665.
- Suomi, S. J., H. F. Harlow, and M. A. Novak (1974). Reversal of social deficits produced by isolation rearing in monkeys. *Journal of Human Evolution* 3(6), 527–534.
- Wallen, K. (1996). Nature needs nurture: The interaction of hormonal and social influences on the development of behavioral sex differences in rhesus monkeys. *Hormones and Behavior* 30(4), 364–378.

Figure 1: Primary Outcomes

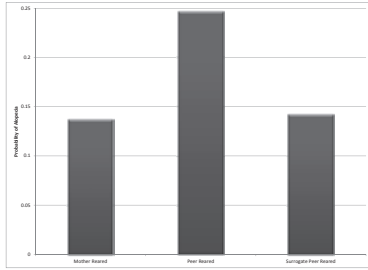
(a) Males: Frequency of Illness



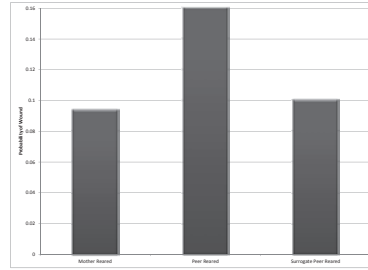
(b) Males: Frequency of Stereotypy



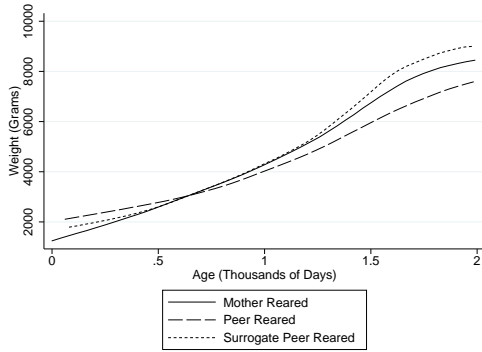
(c) Females: Frequency of Alopecia



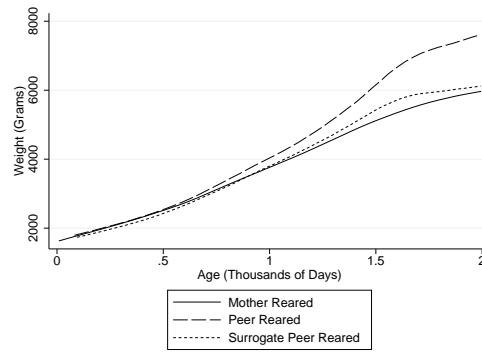
(d) Females: Frequency of Wound



(e) Males: Weight



(f) Females: Weight



Presented above in panels (a)-(d) are predicted frequencies based on the results displayed in Tables 1 and 3. Presented above in panels (e) and (f) are local polynomial regressions for weight over the lifecycle by rearing condition. Weight is measured in grams, and age is measured in 1000s of days.

Table 1: Primary Outcomes, Surrogate Peer Reared vs. Mother Reared

<i>Panel A: Males</i>							
Outcome	<i>Effect</i>			<i>p-Values</i>			
	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Stereotypy	0.215	0.716	0.669	0.000	0.000	0.000	0.000
Frequency of Stereotypy	0.046	0.485	0.478	0.000	0.000	0.000	0.000
Prevalence of Illness	0.723	0.208	0.177	0.003	0.018	0.006	0.025
Frequency of Illness	0.154	0.135	0.120	0.001	0.000	0.000	0.004
Prevalence of Wound	0.385	-0.005	-0.004	0.481	0.386	0.331	0.331
Frequency of Wound	0.052	0.006	0.011	0.399	0.382	0.422	0.570
Prevalence of Alopecia	0.369	0.217	0.156	0.028	0.038	0.038	0.150
Frequency of Alopecia	0.113	0.053	0.041	0.106	0.088	0.066	0.387

<i>Panel B: Females</i>							
Outcome	<i>Effect</i>			<i>p-Values</i>			
	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Stereotypy	0.070	0.756	0.656	0.000	0.000	0.000	0.000
Frequency of Stereotypy	0.015	0.386	0.352	0.000	0.000	0.000	0.000
Prevalence of Illness	0.649	0.220	0.157	0.013	0.009	0.067	0.210
Frequency of Illness	0.161	0.082	0.075	0.035	0.027	0.029	0.160
Prevalence of Wound	0.509	0.056	0.026	0.327	0.247	0.385	0.746
Frequency of Wound	0.094	0.008	0.006	0.397	0.380	0.378	0.680
Prevalence of Alopecia	0.403	0.249	0.116	0.023	0.012	0.181	0.322
Frequency of Alopecia	0.137	0.035	0.005	0.202	0.187	0.522	0.522

Note: $n=94$ for males, 80 for females. p -values below 0.1 are in bold. Uncond. = unconditional difference in means between the treatment and the control group. The corresponding p -values are computed in the columns “Asympt.” and “Naive Permut.”. Condit. = conditional treatment effect with linear covariates year of birth and total time spent in the primate center. The corresponding p -value is computed in the column “Condit. Permut.”. Asympt. = one-sided p -values for the hypothesis of no treatment effect based on asymptotic inference - estimated effect size in the “Uncond.” column. Naive Permut. = one-sided p -values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the “Uncond.” column. Condit. Permut. = one-sided p -values for the hypothesis of no treatment effect based on the Freedman-Lane procedure, using the linear covariates year of birth and total time spent in the primate center, and restricting permutation orbits within strata formed by being first or later born - estimated effect size in the “Condit.” column. Cond. Perm. (Adj.) = p -values from the previous column, adjusted for multiple inference using the stepdown procedure.

Table 2: Primary Outcomes, Surrogate Peer Reared vs. Mother Reared, Males

<i>Panel A: Main vs. Other Illness</i>										
Outcome	<i>Effect</i>				<i>p-Values</i>					
	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Illness - Main	0.723	0.001	-0.020	0.496	0.602	0.492	0.492	0.602	0.492	0.492
Frequency of Illness - Main	0.150	0.084	0.072	0.028	0.017	0.031	0.178	0.017	0.031	0.178
Prevalence of Illness - Other	0.200	0.352	0.311	0.001	0.000	0.001	0.006	0.000	0.001	0.006
Frequency of Illness - Other	0.029	0.072	0.066	0.006	0.002	0.002	0.038	0.002	0.002	0.038

<i>Panel B: Diarrhea vs. Non-Diarrhea Illness</i>										
Outcome	<i>Effect</i>				<i>p-Values</i>					
	Control Mean	Uncond.	Condit.	Asympt.	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)	Naive Permut.	Condit. Permut.	Con.Per. (Adj.)
Prevalence of Illness - Main	0.723	0.001	-0.020	0.496	0.602	0.492	0.492	0.602	0.492	0.492
Frequency of Illness - Main	0.150	0.084	0.072	0.028	0.017	0.031	0.178	0.017	0.031	0.178
Prevalence of Illness - Other: Diarrhea	0.046	0.230	0.216	0.007	0.003	0.004	0.037	0.003	0.004	0.037
Frequency of Illness - Other: Diarrhea	0.004	0.025	0.024	0.015	0.001	0.003	0.059	0.001	0.003	0.059
Prevalence of Illness - Other: Non-Diarrhea	0.154	0.225	0.196	0.016	0.004	0.017	0.128	0.004	0.017	0.128
Frequency of Illness - Other: Non-Diarrhea	0.025	0.047	0.042	0.026	0.013	0.020	0.172	0.013	0.020	0.172

Note: $n=94$ for males, 80 for females. p -values below 0.1 are in bold. Control = MR. Uncond. = unconditional difference in means between the treatment and the control group. The corresponding p -values are computed in the columns “Asympt.” and “Naive Permut.”. Condit. = conditional treatment effect with linear covariates year of birth and total time spent in the primate center. The corresponding p -value is computed in the column “Condit. Permut.”. Asympt. = one-sided p -values for the hypothesis of no treatment effect based on asymptotic inference - estimated effect size in the “Uncond.” column. Naive Permut. = one-sided p -values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the “Uncond.” column. Condit. Permut. = one-sided p -values for the hypothesis of no treatment effect based on unconditional permutation inference - estimated effect size in the “Uncond.” column. Permut. = one-sided p -values for the hypothesis of no treatment effect based on the Freedman-Lane procedure, using the linear covariates year of birth and total time spent in the primate center, and restricting permutation orbits within strata formed by being first or later born - estimated effect size in the “Condit.” column. Condit. Perm. (Adj.) = p -values from the previous column, adjusted for multiple inference using the stepdown procedure. Notice the multiple hypothesis testing correction also includes the other outcomes in Table 1, see Tables A2 and A3 in the Web Appendix for the full set of results.

Table 4: Primary Outcomes, Weight

	Male	Female
Peer Reared	-99.051 (98.838)	473.147** (231.384)
Surrogate Peer Reared	92.234 (173.340)	-152.061 (174.721)
Observations	1420	1217

Note: Weight is a continuous variable measured in grams. Included above are the coefficients δ_1 and δ_2 from a linear regression, estimated by ordinary least squares, of the following form: $Y_{i,t} = \alpha + \delta_1 D_{i,PR} + \delta_2 D_{i,SPR} + \beta X_{i,t} + e_{i,t}$, where $Y_{i,t}$ is the weight of monkey i at time t , $D_{i,PR}$ and $D_{i,SPR}$ are two dummies for treatment status (we set MR as the baseline), and X is a set of basic controls which include dummies for year of birth, a binary indicator for firstborn, and age at the time of the exam. Included in parentheses are robust standard errors, clustered at the individual level to account for repeated observations on the same monkey. Peer Reared and Surrogate Peer Reared are binary indicators of the respective rearing statuses ($D_{i,PR}$ and $D_{i,SPR}$, respectively). * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$.