Early life environments and cognition in adulthood: New evidence using a semiparametric approach and quantile regression

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A R T I C L E   I N F O

Keywords:
- Early life environments
- Cognition
- Semiparametric regression
- Quantile regression
- UK Biobank

A B S T R A C T

Theories and empirical evidence document the importance of early life environmental factors on later life cognition. A next question is how and in what dimension associations between early life environments and later life cognition vary. Using data from the UK Biobank in conjunction with time-place-specific infant mortality rates, we assessed heterogeneous and non-linear associations between early life conditions and later life cognition. We found that the association between the infant mortality rate and later life cognition increased once the UK achieved very low infant mortality rates, suggesting that additional decreases in infant mortality rates in an industrialized society continue to improve later life cognition. We also found that infant mortality rates have stronger effects at upper quantiles of the cognition distribution. This implies that adverse early life environments may have an important role for an early manifestation of cognitive aging.

Introduction

Cognition attracts growing attention in aging societies because changes in cognition may have serious consequences for independent living (Saltz, 2012). Individuals with low cognition need support; therefore, changes in cognition also carry significant consequences for families and societies. Low levels of cognition are accompanied by an increase in physical and psychological toll of family members, who primarily take a caregiving role (Caga et al., 2019; Paradise et al., 2014), and fiscal burden to provide public support (Ton et al., 2017). Understanding major determinants of older age cognition is, therefore, of particular importance to reduce the risk of these unignorable health, social, and economic consequences.

A myriad of potential causes of differences in cognition scatters in many stages over the life course. For example, failing cognition is associated with low socioeconomic status during childhood (Ding & He, 2021), adverse childhood experiences (Ding & He, 2021), exposure to an infectious disease pandemic in mid-life (Wen et al., 2021), lack of exercise (Sofi et al., 2011), loneliness (Boss et al., 2015), disadvantaged neighborhood (Ailshire et al., 2017), and the progression of age (Plassman et al., 2010). By contrast, failing cognition is less prevalent among those with higher socioeconomic status during childhood (Zhang et al., 2020), better educational attainment (Fletcher et al., 2021; Schneeveis et al., 2014; Zhang et al., 2020), greater participation in cognitively oriented extracurricular activities (Greenfield et al., 2022), and social and intellectual stimulation at home in childhood (Ramírez-Luzuriaga et al., 2021). While these studies demonstrated the presence of potential causes of differences in cognition in many stages over the life course, a growing literature stresses the role of adverse environments in critical periods—prenatal and early postnatal periods in which an organism is very sensitive to environmental stimuli.

The developmental origins of health and disease (DOHaD)—alternatively Barker’s hypothesis, biological imprint hypothesis, and biological embedding—is a predominant theoretical framework for the understanding of how environments in critical periods are associated with later life health. Theories posit that exposures to adverse environments in critical periods permanently and irreversibly alter one’s biological functions, which in turn have long-lasting effects on health outcomes over the life course (Barker, 2007; Ben-Shlomo & Kuh, 2002; Hertzman & Boyle, 2010; Montez & Hayward, 2011). Cognition is not an exception; empirical evidence showed the importance of experiences during critical developmental periods for later life cognition (e.g., Case & Paxson, 2009; Cook & Fletcher, 2015; de Rooij et al., 2010; de Groot et al., 2011; van den Berg et al., 2010; Xu et al., 2018).
using infant mortality rate, a measurement representing a complex result of multiple environmental factors including, but not limited to, postnatal nutritional intake, exposure to infection, maltreatment, abuse, and other adverse conditions, Schiman et al. (2019) found that an increase in the infant mortality rate in the birth year is associated with a decrease in future cognitive test score.

With accumulated empirical evidence for the associations between early life environments and later life cognition, a next question is how and in what dimension these relationships differ. Despite emerging empirical evidence for the heterogeneous associations between early life environments and later life cognition (e.g., Cook & Fletcher, 2015), many important research questions are still unresolved. Using time-region-specific infant mortality rates as a measure of early life environments in a critical developmental period, the current study contributes to this discussion in two ways. First, we investigate how the association between early life environments and later life cognition depends upon the severity of early life environments. Much prior research has (implicitly) assumed that a unit improvement in early life environments (i.e., a point decrease in infant mortality rate in this study) is associated with a constant improvement in later life cognition. Nonetheless, this is a critical assumption that there are several plausible scenarios that do not satisfy this linearity assumption. For example, a unit improvement in very severe early life environments is probably more crucial for later life cognition than a unit improvement in less severe early life environments. In this case, the association between infant mortality rate and later life cognition would be more pronounced when infant mortality rate is higher. By contrast, if a unit improvement in severe early life environments is less critical, the association between infant mortality rate and later life cognition would be stronger when infant mortality rate is lower (for graphical representation, see Fig. 1). Relaxing the linearity assumption may provide important implications, especially for industrialized societies that have already achieved very low infant mortality rates. Specifically, our effort to relax this assumption will document whether additional investment to achieve the even lower infant mortality rates in these societies would contribute to an improvement in later life cognition.

Second, we will investigate at which level of cognition early life environments are associated. Whereas previous research provided empirical evidence for “on average” associations between early life environments and later life cognition, little is known about how these associations vary across the distribution of cognition.1 Addressing this limitation will deepen our understanding of associations between early life environments and later life cognition. For instance, if the difference in cognition by infant mortality rates is larger for adults at higher quantiles of cognition than for those at lower quantiles, early life environments may be more consequential for an early manifestation of cognitive aging. By contrast, a larger difference in cognition for adults at lower quantiles suggests the possibility that effects of early life environments less likely appear until cognitive aging proceeds to some extent.

There are several theoretical and empirical reasons to expect sex differences in the consequences of early life environments. For example, the fragile male hypothesis (Kraemer, 2000) posits that males are more vulnerable to early life environments than females. Empirical evidence supporting this claim can be found in Quaranta’s (2014) findings which showed higher mortality rates for males than for females among adults who were exposed to disease in early life. By contrast, prior research also found that women who experienced early life exposures on later life health is more serious for females than for males (Mu & Zhang, 2011). These theory and empirical evidence lead us to posit the presence of sex differences in above-mentioned heterogeneous associations between infant mortality rate and later life cognition. Nonetheless, we are uncertain how the heterogeneous associations differ by sex because scholarly consensus has not been made yet for the sex differences in the consequences of early life environments.

The goal of the current study is to explore the above-mentioned potential differences in associations between early life environments and later life cognition. More specifically, we answer the following research questions: (1) How does the association between infant mortality rate and later life cognition depend on the severity of infant mortality rate? (2) How does the association between infant mortality rate and later life cognition depend on the level of cognition? (3) Do the associations in (1) and (2) differ by sex?

Data and methods

Data

We used data from the UK Biobank (UKB) in conjunction with data on geographical boundaries of counties and district-level infant mortality rate produced by A Vision of Britain through Time (https://www.visionofbritain.org.uk/). The UKB is a large-scale biobank study of over 500,000 people that collected baseline data from 2006 to 2010. Respondents’ age ranges from 37 to 74 years at the time of survey. The UKB is suited well to our purposes because it includes an objective cognitive test score as well as coordinate information of the place of birth, which is required information to cross-walk time-place-specific infant mortality rate. A Vision of Britain through Time provides geographical boundary data for administrative counties as of 1931, 1951, 1961, and 1971 and the year-specific number of births and deaths under age 1 at the district level with the administrative county information from 1911 to 1974.2 Of completed respondents in the UKB (n = 502,505), we excluded those who do not have a cognition measure (n = 297,348), infant mortality rate (n = 31,878), and covariates (n = 1117), which left us an analytical sample of 172,162 (see Fig. 2).

Variables

Cognition

Our dependent variable is a measure of cognition (fluid intelligence).3 The UKB constructed a measure of cognition by summing the number of correct answers in 13 logic puzzles in 2 min. This measure is only available for less than half of UKB participants because the module of the cognition test was added at the end of the recruitment window.

Infant mortality rate

We used a mortality table (“mort_lgd_ew”) provided by A Vision of Britain through Time to construct a measure of infant mortality rate—the number of deaths below age 1 for every 100 live births. Because the infant mortality rates were collected annually while the boundary information was available only for census years (i.e., 1931, 1951, 1961, and 1971), we classified respondents into counties by using the boundary data of the year nearest to the birth year, except for the infant mortality rate in 1965, the year that Greater London was established. We excluded UKB respondents born outside of England and Wales because of the lack of infant mortality data. Additionally, we also excluded some England and Wales natives who were born in places that the boundary data did not cover.

We constructed month-year-county-specific infant mortality rate using the following equations:

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1 An exceptional study examined differences in the association between an early life factor and children’s cognition at different quantiles of a cognitive test (Koh, 2017); however, we are unaware of prior studies that focused on adults.

2 A Vision of Britain through Time also provides geographical boundary data at the district level; however, the data are not publicly available.

3 For details, see https://biobank.nihr.ac.uk/showcase/field.cgi?id=20016.
where the infant mortality rate of county \( c \) in year \( y \) and month \( m \) (\( IMR_{m,y,c} \)) is the weighted sum of the infant mortality rates of place \( c \) in year \( y \) (\( IMR_{y,c} \)) and year \( y-1 \) (\( IMR_{y-1,c} \)). \( \alpha \) in equation (1) represents the weight to adjust the exposure. For example, under the assumption of the gestational period of 10 months, respondents who were born in county \( c \) in February 1950 (\( IMR_{Feb,1950,c} \)) have the weight of 0.2 (\( \frac{2}{10} \)) because they were exposed to the infant mortality rate of county \( c \) in 1950 for two months and that in 1949 for eight months. Although an infant mortality rate is formally defined as the number of deaths under age 1 (\( D_{0,1,y} \)) for every 1000 live births (\( B_{y} \)), we rescaled to the number of deaths under age 1 for every 100 live births to interpret the regression coefficients with three decimal digits.

Control variables

We incorporated age, sex, birth month fixed effect, birth year fixed effect, and region of birth fixed effect as control variables. Birth year and month fixed effects account for periodic, cohort, and seasonal differences, whereas region of birth fixed effect accounts for the possible confounding of unmeasured regional characteristics.\(^4\) Region of birth fixed effect is a nine-category measure, including East Midlands, East of England, London, North East, North West, South East, South West, Wales, West Midlands, and Yorkshire and The Humber. Because we do not have publicly available region-level boundary data in the years in which respondents were born, we used geographical boundary for the 2011 census (http://infuse.ukdataservice.ac.uk/). There were 1117 respondents whose birthplaces were not covered by the region-level boundary data. We excluded them from our analyses because they are only 0.6% of the total analytical sample.

Model specification

To address our research questions, we began with a semi-parametric regression method:

\[
Y_i = \alpha + f(\text{IMR}_{m,y,c}) + \gamma \cdot X_i + \theta_y + \phi_x + \delta_r + \epsilon_i
\]

where cognition (\( Y_i \)) is a function of infant mortality rate (\( IMR_{m,y,c} \)). We also incorporated control variables (\( X_i \)), including respondents’ age at the time of survey and sex, birth month fixed effect (\( \theta_y \)), birth year fixed effect (\( \phi_x \)), and region of birth fixed effect (\( \delta_r \)). Using the regression equation above, we also conducted statistical tests with parametric models of whether there are statistically significant relationships between infant mortality rates and later life cognition. Using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC), we compared the goodness of fit of parametric models. We then estimated unconditional parametric quantile regressions using the same regression equation to test our second research question.\(^5\) With regard to the standard errors, we used clustered-robust standard errors with an assumption that errors are correlated within the county of birth (i.e., geographical unit of the infant mortality rate measure). Table 1 presents descriptive statistics for all variables in our analytical sample.

\(^4\) We did not include a county (or district) of birth fixed effect because adding many fixed effects will inflate standard errors and reduce the statistical power. Further, our key independent variable—infant mortality rate—is defined at the county level; therefore, adding county of birth fixed effect will substantially reduce statistical power.

\(^5\) We used unconditional quantile regressions because we included control variables. For more methodological details, see Killewald and Bearak (2014).
Results

Differences by the severity of adverse early life environments

To address our first research question, we estimated a semiparametric regression for the relationship between infant mortality rate and later life cognition. Fig. 3 illustrates the results of the semiparametric regression. The figure shows a non-linear association between infant mortality rate and later life cognition. Specifically, a unit increase in the infant mortality rate is associated with the cognitive test score more substantially and consistently when the infant mortality rate is lower than 3. The association between a unit increase in infant mortality rate and the cognitive test score declines as the infant mortality rate increases, and we no longer observe a negative relationship if the infant mortality rate is around 6. Given that the infant mortality rates before 1945 were higher than 4 in most counties (see Fig. 4), a decrease in infant mortality rate before and during World War II is less associated with an improvement in later life cognition. By contrast, the decline in infant mortality rates after the late-1950s more likely contributes to the improvement in later life cognition because most counties had achieved infant mortality rates of below 3.

Because we cannot conduct significance tests for the relationship between infant mortality rate and later life cognition in the semiparametric method, we then turn to assess the relationship by using four functional specifications—linear, quadratic, cubic, and logarithmic. Table 2 presents the results of OLS regressions for the cognitive test score by using four different functional specifications. Among the four specifications, a linear specification fits the worst based on AIC and BIC. It is important to note that the infant mortality rate is not significantly associated with the later life cognition test score in a linear specification. This raises a concern of model misspecification, suggesting that a unit improvement in adverse early life environments is not associated with later life cognition in a homogeneous manner. By contrast, the regression coefficients of the infant mortality rate and infant mortality rate squared in a quadratic specification reach the 5% significance level. This finding is consistent with our results of the semiparametric regression because the negative effects of infant mortality rate on the cognitive test score are present when the infant mortality rate is low (see Supplementary Fig. 1). A similar association can be seen in a logarithmic

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6 Because inclusion of respondents who were exposed to very high or very low infant mortality rate will induce an overfitting issue in these ranges of infant mortality rate and make the association between infant mortality rate and cognition invisible, we excluded respondents at the top and bottom 5% of infant mortality rates.

7 We used OLS regressions in all regressions because the outcome variable was treated as continuous. We allowed the relationship between infant mortality rate and cognition to be non-linear by using polynomial infant mortality rate or log-transformed infant mortality rate.
specification in which regression coefficients of log-transformed infant mortality rate are statistically significant.

**Differences by the level of cognition**

Next, we assessed how the association between infant mortality rates and later life cognition varies by the level of cognition. Fig. 5 presents the estimated regression coefficients from the quantile regression for a quadratic specification (estimated regression coefficients are available in Supplementary Table 1). The regression coefficients of linear term are statistically significant across the quantiles; however, the size of regression coefficient increases as the percentile in the cognitive test score increases. Additionally, the size of regression coefficients for the quadratic term also increases as the percentile in the cognitive test score increases. Even if we consider the 95% confidence intervals of the estimated associations, some differences in the size of regression coefficients (e.g., between 10th and 90th percentile) are unignorable.

To assess the robustness of our results to the model specifications, we also conducted the same analyses for linear, cubic, and logarithmic specifications. The results of these analyses are presented in
Table 2: Estimated coefficients from OLS regressions for the cognition test score (N = 172,162).

| VARIABLES                  | Linear       | Quadratic   | Cubic        | Logarithmic |
|----------------------------|--------------|-------------|--------------|-------------|
| Infant mortality rate      | -0.063       | -0.271***   | -0.409*      |             |
|                            | (0.041)      | (0.098)     | (0.196)      |             |
| Infant mortality rate      | 0.020*       | 0.053       |              |             |
| squared                    | (0.009)      | (0.037)     |              |             |
| Infant mortality rate      | -0.002       |             |              |             |
| cubed                      | (0.003)      |             |              |             |
| Logged infant mortality    | -0.481*      |             |              |             |
| rate                      | (0.222)      |             |              |             |
| Constant                   | 14.937***    | 15.465***   | 15.643***    | 15.491***   |
|                            | (2.493)      | (2.498)     | (2.549)      | (2.459)     |
| AIC                        | 735,759      | 735,737     | 735,735      | 735,741     |
| BIC                        | 736,542      | 736,340     | 736,338      | 736,334     |

Note: Additional controls are not shown. Standard errors are in parentheses and are clustered at county of birth. AIC and BIC represent Akaike Information Criteria and Bayesian Information Criteria. ***p < 0.001, **p < 0.01, *p < 0.05, |p < 0.1.

Supplementary Table 2.4. Although we do not see substantial differences across quantiles in a linear specification, the size of regression coefficients increases as the percentile in the cognitive test score increases in the cubic and logarithmic specifications, consistent with the findings with a quadratic specification. Furthermore, the differences in the effect size in the cubic specifications are also substantially large even after standard errors are taken into consideration. Overall, these provide additional empirical evidence for the potential differences in the relationship between infant mortality rates and later life cognition by the level of cognition.

Sex differences

We then turned to assess how the heterogeneous associations between infant mortality rate and later life cognition differ by sex. With regard to the heterogeneous associations by severity of infant mortality rate (see Online Appendix I), a logarithmic specification is best-fitted for males. For females, a quadratic specification is best-fitted. Given that these non-linear models suggest the presence of heterogeneous associations between infant mortality rate and later life cognition by the severity of infant mortality rate. Furthermore, Supplementary Figure A1.1 in Online Appendix I demonstrates subtle sex differences in the association between infant mortality rate and later life cognition. For the heterogeneous associations by the level of cognition (see Online Appendices II and III), there is an increase in the size of regression coefficients corresponding to an increase in the quintile of cognition in a logarithmic specification both for men and for women. Although we can see somewhat clearer differences in the association between infant mortality rate and later life cognition by the quintile of cognition for women than for men, overall heterogeneous associations by the level of cognition are not substantially different by sex.8

Discussion

The goal of this study is to assess how the association between adverse early life environments and later life cognition depends upon the severity of adverse early life environments and the level of cognition. Using the semiparametric regression method, which requires no parametric assumptions, our first finding demonstrated that the association between early life environments and later life cognition substantially differs by the severity of adverse early life environments. An association between a unit improvement in infant mortality rate and later life cognition is larger after the UK achieved low infant mortality rates. These findings provide an important implication for the findings in earlier work (Case & Paxson, 2009; Schiman et al., 2019), which concluded that associations between infant mortality rates and later life cognition are statistically significant, but very small. These small associations are probably because of their focus on the period in which infant mortality rates were still high. For example, Case and Paxson (2009) restricted their analytical sample to U.S. cohorts born between 1910 and 1950. Similarly, Schiman et al. (2019) focused on World War II birth cohorts in Britain. Given the high infant mortality rates in these periods, their analyses might mask more substantial associations between early life environments and later life cognition after the U.S. and UK achieved a lower infant mortality rate.

Our findings of the differences in the association between early life environments and later life cognition by the severity of early life environments also have several important substantive implications. First, additional investment to reduce the risk of infant mortality may contribute to the improvement in cognition of adults in the long run because we observed clear negative associations between infant mortality rates and later life cognition after the UK achieved low infant mortality rates. Second, our findings also serve to generate a hypothesis of what early life environmental factors are associated with later life cognition. Specifically, we hypothesize that advances in obstetric and neonatal care for high-risk pregnancies and preterm births improved the cognition of adults because the recent decline in infant mortality rates in developed countries is primarily due to the technological development in these medical fields (Andrews et al., 2008). By contrast, an increase in standards of living and a decrease in infectious disease, which are the causes of the decline in infant mortality rate in early stage (Andrews et al., 2008), may be less important for later life cognition.

Further, we also investigated how associations between infant mortality rates and later life cognition are contingent upon the level of cognition. We found stronger associations between infant mortality rates and later life cognition among those with a higher cognition level than those with a lower cognition level. One important implication of this finding is that environmental factors in the critical periods are crucial for the differences in an early-stage of cognitive aging or before the onset of cognitive aging, but probably less if cognitive aging has already proceeded to some extent.

We also assessed sex differences in the heterogeneous associations. Although there were somewhat clearer heterogeneous associations for women than for men, we found that heterogeneous associations by the severity of early life environments and the level of cognition both for men and for women. Whereas a theory and empirical evidence showed the presence of sex differences in the consequences of early life environments on later life health (Kraemer, 2006; Mu & Zhang, 2011; Quaranta, 2014), these findings imply that sex is probably a less crucial axis for when and at which level early life environments affect later life cognition.

We acknowledge several limitations in the current study. First, our analytical sample only includes a subsample of the UKB, which has a cognition measure. This reduces the statistical power of our analyses, and non-random sample selection may induce biased estimates.10 However, the UKB is still one of the largest datasets with an objective

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8 Note that the regression coefficients for women at the 40th percentile are very large, but their standard errors are also large. Further, we did not see these large regression coefficients at 39th and 41st percentiles. Therefore, this is not empirical evidence to question our findings that an increase of quantile is associated with a larger size of regression coefficient.

9 Based on the synthetic cohort life table in 1950 in the U.S., the infant mortality rate in our definition was 3.17. The synthetic cohort life table is publicly available at Human Mortality Database (https://www.mortality.org/).

10 Auxiliary tests also showed the presence of systematic differences of the missingness of the cognition measure in age, sex, and educational attainment after controlling for survey date and place. The non-random missingness in these characteristics may also induce post-treatment bias.
Fig. 5. Estimated coefficients from unconditional quantile regressions for the cognition test score.
Note: Additional controls include age, sex, birth year fixed effect, birth month fixed effect, and region of birth fixed effect. Dots and error bars represent estimated regression coefficients and their 95% confidence intervals.
contribute to a deceleration of cognitive aging for older adults. We also found the impacts of early life environments are stronger for environments are less severe, like contemporary industrialized nations. This unequal probability may induce spurious relationships between infant mortality rate and later life cognition.

Conclusion
Life course theories are a predominant theoretical framework in the contemporary health sciences. Health scholars have long acknowledged the importance of environments in critical periods given its long-lasting effects on later life health (Barker, 2007; Ben-Shlomo & Kuh, 2002; Hertzman & Boyce, 2010; Montez & Hayward, 2011). To extend this scholarly discussion, we used a semi-parametric approach and quantile regression to assess how associations between environments experienced during critical periods and later life cognition differ by the severity of early life environments and the level of cognition in the UK.

Our findings suggest that the association between early life environments and later life cognition is more pronounced when early life environments are less severe, like contemporary industrialized nations. We also found the impacts of early life environments are stronger for those in an early-stage of cognitive aging. Taken together, these results imply that improvements in environments in critical periods may contribute to a deceleration of cognitive aging for older adults in developed nations.

The current study is the first to document how the associations between early life environments and later life cognition are dependent on the severity of early life environments and the level of later life cognition. Our findings shed light on when and at which level of cognition early life environments take an important role for later life cognition. Investigating whether similar heterogeneous associations can be seen in other health outcomes will make the discussion of the potential importance of environments in critical periods move forward.

Author contributions
Shiro Furuya: Conceptualization, Methodology, Software, Formal analysis, Investigation, Writing – Original Draft, Visualization. Jason M. Fletcher: Conceptualization, Methodology, Resource, Writing – Review & Editing, Supervision.

Declaration of competing interest
None.

Data availability
The authors do not have permission to share data.

Acknowledgment
This research was supported by the National Institute on Aging (RF1 AG062765). The authors gratefully acknowledge use of the facilities of the Center for Demography of Health and Aging at the University of Wisconsin—Madison, funded by National Institute on Aging Center Grant P30 AG017266. This research has been conducted using the UK Biobank Resource under Application 57284. The authors also thank Sherry Huhn for exceptional editorial assistance.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2022.101251.

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