Elevated levels of protein in urine in adulthood after exposure to the Chinese famine of 1959–61 during gestation and the early postnatal period

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Abstract

Background: Animal models have suggested that undernutrition during gestation and the early postnatal period may adversely affect kidney development and compromise renal function. As a natural experiment, famines provide an opportunity to test such potential effects in humans. We assessed whether exposure to the Chinese famine of 1959–1961 during gestation and early postnatal life was associated with the levels of proteinuria among female adults three decades after exposure to the famine.

Methods: We measured famine intensity using the cohort size shrinkage index and we constructed a difference-in-difference model to compare the levels of proteinuria, measured with a dipstick test of random urine specimens, among Chinese women (n = 70,543) whose exposure status to the famine varied across birth cohorts (born before, during or after the famine) and counties of residence with different degrees of famine intensity.

Results: Famine exposure was associated with a greater risk [odds ratio (OR) = 1.54; 95% confidence interval (CI): 1.04, 2.28; P = 0.029] of having higher level of proteinuria among women born during the famine years (1959–61) compared with the unexposed post famine-born cohort (1964–65) in rural samples. No association was observed among urban samples. Results were robust to adjustment for covariates.

Conclusions: Severe undernutrition during gestation and the early postnatal period may have long-term effects on levels of proteinuria in humans, but the effect sizes may be small.

Key words: Barker hypothesis, natural experiment, maternal undernutrition, famine, proteinuria, renal function
Introduction

The Barker hypothesis proposes that an adverse intrauterine environment elevates the risk for chronic disease development later in life.\(^1\) It has become increasingly evident that undernutrition during gestation and the early postnatal period may result in the abnormal development of some organs, including the kidney.\(^2\)\(^-\)\(^4\) Previous studies have found that maternal undernutrition was associated with a reduced number of glomeruli, which can elevate the risk for hyperfiltration injury, microalbuminuria (MA) and end-stage renal disease.\(^5\)\(^,\)\(^6\)

Experimental data on laboratory animals suggest that prenatally undernourished rats have a higher likelihood of developing renal disease,\(^7\) and maternal protein-energy malnutrition in sheep significantly increases the risk of failure of kidney function in adult offspring.\(^8\) Studies in human subjects also suggest similar links between low birthweight, a marker of intrauterine growth retardation, and the development of renal disease or compromised kidney function.\(^3\) Low birthweight was associated with an elevated risk of microalbuminuria in Australian Aborigines,\(^9\) abnormal glomerular filtration rate in Dutch adolescents\(^10\) and end-stage renal disease in adults in the USA\(^11\) and Norway.\(^12\)

A recent cohort study on the Dutch famine of 1944–45 was the first to provide direct evidence suggesting that famine exposure during mid-gestation may prevent the sufficient formation of glomeruli at birth and increase the risk of microalbuminuria in adulthood, although the study failed to reach a conclusion regarding end-stage renal disease risk, due to the small sample size.\(^5\) As a natural experiment, the Chinese famine of 1959–61 presents another opportunity to evaluate the impact of severe undernutrition \textit{in utero} and/or during early postnatal life on adult diseases.\(^13\)\(^,\)\(^14\) Unlike the Dutch famine that was imposed on a previously well-nourished population, the Chinese famine affected individuals who were already experiencing chronic undernutrition and impoverishment.\(^14\)

The Chinese famine of 1959–61 was unearthed in the 1980s by scholars who inferred from census data that up to 30 million people were ‘missing’ from birth cohorts during this time.\(^14\)\(^-\)\(^16\) The famine was caused by massive institutional and policy changes during the Great Leap Forward campaign launched in 1958, which aimed at achieving a rapid industrialization at the expense of agriculture; weather may have aggravated the problem in some areas.\(^14\)\(^,\)\(^17\) These radical reforms immediately resulted in a substantial drop of grain output and caused a nationwide food shortage, and the estimated availability of food energy during the 3 following years decreased to 1500 calories daily per capita, far below average food energy requirements (~2100 calories).\(^15\)\(^,\)\(^18\) Dramatic variations in famine intensity existed across regions, with rural areas experiencing a disproportionate impact of the famine and the highest severity occurring in Sichuan and Anhui provinces,\(^14\)\(^,\)\(^18\)\(^,\)\(^19\) where extreme behaviours such as eating tree bark and cannibalism were reported. Failure to respond in time to the severe food shortage contributed to the famine lasting until the end of 1961 in most regions and until as late as 1962 in some rural areas. The famine caused a substantial excess mortality of approximately 30 million deaths and a fertility reduction by 30 million lost births during this period, as seen in Figure 1.\(^15\)\(^,\)\(^18\)\(^,\)\(^20\)

In the present study, we investigated the associations between early life exposure to the Chinese famine of 1959–61 and levels of protein in urine in adulthood among a large sample of Chinese women born before, during or Figure 1. Fertility reduction and excess death rate and infant mortality (per thousand) during the Chinese Famine of 1959-61. Sources: computed from the 1982 Population Census of China and the 1988 Two-Per-Thousand National Survey of Fertility and Contraception.
after the famine. We assessed the associations by birth cohorts separately for urban and rural residents.

Methods

Data, study sample and measurements

Data were derived from the China-U.S. Collaborative Project for Neural Tube Birth Defect Prevention conducted from 1993 to 1996, which examined the efficacy of periconceptual folic acid supplementation on preventing neural tube birth defects in China. The project was conducted by the U.S. Centers for Disease Control and Prevention and the Peking University Health Science Center. Chinese women living in Hebei, Zhejiang and Jiangsu provinces who were preparing for marriage registration were enrolled. Upon enrolment, a questionnaire documenting basic demographics, socio-economic status and general health conditions was completed by each participant. Anthropometric measures were obtained following standard protocols, and body weight and height were measured without shoes or heavy clothing using a calibrated scale. The body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square metres). Hypertension was diagnosed by medical staff (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg). Urine samples were obtained by medical staff on the morning of a clinical visit after an overnight fast, and dipstick testing was conducted on a fresh, morning first-void urine sample, with the colour indicator turning from yellow to green progressively classifying urinary albumin concentration as negative, trace (5 to 20 mg per dl), 1+ (30 mg per dl), 2+ (100 mg per dl) or 3+ (300 mg per dl).

We restricted the study to cohorts born from 1957 to 1965. The China-U.S. Collaborative Project for Neural Tube Birth Defect Prevention recruited primarily young women at their fertility peak and very few women born before 1957 were included. We divided these women into the following groups: (i) those born before the famine, in 1957–58 (the ‘pre-famine’ birth cohort) who were likely exposed to the famine during early postnatal life; (ii) those born in 1959–61 (the ‘famine’ birth cohort) who were likely exposed both before and during the famine years (1959–61), labeled \( N_{\text{famine}} \), and the mean size of cohorts born during the famine years (1959–61), labeled \( N_{\text{famine}} \). We then generated the CSSI as the difference between \( N_{\text{nonfam}} \) and \( N_{\text{famine}} \) divided by \( N_{\text{nonfam}} \). The validity and reliability of CSSI as a single famine intensity indicator has been tested and discussed elsewhere.

Among the 35 sampled counties, the CSSI ranged from 0.24 to 0.64, with a mean of 0.42 and a standard deviation of 0.09, indicating that on average the population size in 1990 of adults who were born during the 3 years of the famine was 42% smaller compared with that of adults born during the 3 years immediately preceding or following the famine. Previous studies have suggested that the population size shrinkage among birth cohorts born during the famine years was primarily due to the fertility reduction and excess infant mortality during that time. The purpose of the CSSI was to account for the famine severity in a particular region, which likely had a direct effect on famine exposure of an individual born in that region.

Statistical analysis

We used the variation of famine exposure across cohorts and regions to construct a difference-in-difference (DID) estimator and fitted ordered logit (proportional-odds cumulative logit) models for the ordinal levels of protein concentration in urine with the DID estimator as shown below:

\[
\text{logit}(\Pr(P_{rk} \leq j | \text{CSSI}_r, \text{Cohort}_k)) = B_0 + \varphi_r \text{region}_f + \gamma \text{Log(CSSI)}_r + \sum_{k=1}^{3} \beta_k (\log (\text{CSSI}_r \times \text{Cohort}_k)) + V_{rk}
\]

where \( P_{rk} \) refers to the level of protein concentration in urine (\( j = 0 \) refers to negative (reference level), \( j = 1 \) refers to trace level, \( j = 2 \) refers to 1+ level and \( j = 3 \) refers to 2+ and above level) for an individual born in county \( r \) and period \( k \) (\( k = 1 \) refers to birth years 1957–58, \( k = 2 \) refers to birth years 1959–61, \( k = 3 \) refers to birth years 1962–63).
and the reference group refers to unexposed cohorts born in 1964–65). \( z_k \) is the cohort fixed effect, \( \phi_f \) is the region fixed effect and \( CSSIr \) is the cohort size shrinkage index in county \( r \). A log value of \( CSSI \) was taken for a better model fit. \( \beta_k \), the coefficient of the interaction between the cohort size shrinkage index and the cohort dummy variables, captures the famine effect as a ‘treatment’ effect in a standard DID model. A detailed discussion on estimating ‘treatment’ effect using the interaction term in non-linear DID models was presented elsewhere.\(^{25,26}\) To estimate the average effect across 35 sampled counties, we multiplied the interaction coefficient by 0.57, the mean of the log values of \( CSSI \) across all counties. In addition, \( VX_{irk} \) refers to a spectrum of covariates including ethnicity (\( han \) Chinese or minority), height, BMI-based weight status (<18.5 as underweight, 18.5–24.9 as normal, 25.0–29.9 as overweight and >30.0 as obese), hypertension (>140/90 mmHg), education (elementary school, junior high school, or high school and above) and occupation (farmer or other), which were included in the full model to estimate the adjusted odds ratio. We also included month of birth in addition to year of birth (\( Cohort \ k \)) to control for birth seasonality. Standard error was adjusted for clustering by county. Cases with missing information for any of the variables included in the analysis were excluded (\( n = 14,002, 19.8\% \)). Analysis suggested no significant differences in the measured characteristics between the excluded cases with missing data and those included in the sample for analyses. All analyses were conducted separately for the rural (\( n = 65,184 \)) and urban (\( n = 5,359 \)) samples using Statistical Analysis Software (SAS Version 9.0).

### Table 1. Characteristics of the study sample

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Rural sample ( (N = 65,184) )</th>
<th>Urban sample ( (N = 5,359) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm, mean and SD)</td>
<td>158.7 (4.5)</td>
<td>159.2 (4.6)</td>
</tr>
<tr>
<td>Province of residence (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hebei</td>
<td>2.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Zhejiang</td>
<td>86.4</td>
<td>81.1</td>
</tr>
<tr>
<td>Jiangsu</td>
<td>11.2</td>
<td>15.5</td>
</tr>
<tr>
<td>Education (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no schooling</td>
<td>5.3</td>
<td>4.3</td>
</tr>
<tr>
<td>elementary school</td>
<td>36.6</td>
<td>19.5</td>
</tr>
<tr>
<td>junior high school</td>
<td>50.3</td>
<td>48.1</td>
</tr>
<tr>
<td>high school and above</td>
<td>7.5</td>
<td>27.5</td>
</tr>
<tr>
<td>missing</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>99.3</td>
<td>99.5</td>
</tr>
<tr>
<td>minority</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>missing</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Occupation (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>farmer</td>
<td>81.5</td>
<td>50.6</td>
</tr>
<tr>
<td>worker</td>
<td>16.7</td>
<td>33.8</td>
</tr>
<tr>
<td>other</td>
<td>1.7</td>
<td>15.1</td>
</tr>
<tr>
<td>missing</td>
<td>0.1</td>
<td>0.5</td>
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<tr>
<td>Weight status (%)</td>
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</tr>
<tr>
<td>underweight</td>
<td>10.7</td>
<td>14.6</td>
</tr>
<tr>
<td>normal weight</td>
<td>79.3</td>
<td>77.8</td>
</tr>
<tr>
<td>overweight</td>
<td>8.2</td>
<td>6.4</td>
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<tr>
<td>obese</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>missing</td>
<td>1.4</td>
<td>0.7</td>
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<tr>
<td>Hypertension (%)</td>
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<td></td>
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<tr>
<td>no</td>
<td>83.3</td>
<td>76.0</td>
</tr>
<tr>
<td>yes</td>
<td>15.9</td>
<td>23.1</td>
</tr>
<tr>
<td>missing</td>
<td>0.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Urine protein concentration (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>75.3</td>
<td>79.1</td>
</tr>
<tr>
<td>trace (5-20 mg/dl)</td>
<td>4.9</td>
<td>6.1</td>
</tr>
<tr>
<td>1 + (30 mg/dl)</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>2 + and above(&gt;100mg/dl)</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>missing</td>
<td>18.3</td>
<td>12.9</td>
</tr>
</tbody>
</table>

not alter this association (OR = 1.53; 95% CI: 1.04, 2.26; P = 0.031). The effect size of 0.23, which equals the Ln (1.53) divided by 1.81,29 is considered small.30 We did not observe an association between the famine exposure and the concentration of protein in urine for the 1957–58 cohort who were born before the famine and exposed during the early postnatal period (OR = 1.29; 95% CI: 0.73, 2.26; P = 0.380). The 1962–63 birth cohort exhibited no statistically significant difference in the levels of proteinuria compared with the unexposed 1964–65 birth cohort (OR = 1.26; 95% CI: 0.99, 1.59; P = 0.051).

In the urban sample (Table 3), we did not find a statistically significant difference in the protein concentration in urine when the cohorts born before the famine (1957–58), during the famine (1959–61) or immediately after the famine (1962–63) were compared with the unexposed 1964–65 birth cohort.

A power analysis (Table 4) indicated that the sample size for rural residents ensured excellent statistical power of 100% to detect the reported associations between famine exposure and levels of proteinuria at a 95% confidence level. For the urban sample, except for the pre-famine cohorts, a two-sided test had less than 80% power to detect those reported odds ratios at 95% confidence. Therefore the null finding for the urban sample could be due to a lack of statistical power and the results regarding urban residents should be interpreted as merely suggestive.

Robustness test of the results

We excluded 18.3% of respondents in the rural sample and 12.9% in the urban sample due to missing data on levels of proteinuria, the outcome variable. To test whether these exclusions may have biased our results, we reanalysed the data using an inverse probability weighting (IPW) estimator, which is considered efficient in addressing a variety of sample selection issues.31 IPW is based on the idea that each individual has some probability (p) of being included in the sample, and that an inverse of this probability (w = 1/p) can be used to weight the sample to account for loss resulting from sample selection. Specifically, we estimated a logistic regression model, predicting the probability of being included in the analytical sample (i.e. having no missing data on the outcome variable). The explanatory variables in the predicting model included age, ethnicity, education, occupation, rural or urban residence, county of residence, height, weight and hypertension status of the women. Then we assigned each respondent a weight that was equal to the inverse of the predicted probability of being included in the analytical model. The weighted sample based on the IPW estimator yielded similar results to those reported above (Table 5), suggesting that sample attrition due to missing data on the outcome variable was unlikely to have biased our results.

Discussion

Although increasing evidence has suggested developmental origins of many chronic diseases such as coronary heart disease and type 2 diabetes,32,33 limited evidence has been reported on undernutrition in early life due to famine exposure and the subsequent impact on renal function in adult life.5 Based on a large sample of Chinese women born before, during and after the Chinese famine of 1959–61, we found that rural women born during the famine had an elevated risk of having a higher level of proteinuria three decades after exposure to the famine; these results were independent of weight and hypertension status. Our findings were consistent with those of a previous study on the Dutch famine, which concluded that people who were exposed to famine during mid-gestation had a higher rate of microalbuminuria (defined as albumin/creatinine ratio ≥2.5 g/mmol) compared with those who were not prenatally exposed to famine (OR = 2.1; 95% CI: 1.0, 4.3), and adjustment for cardiovascular confounders including hypertension and obesity did not attenuate this association (adjusted OR = 3.2; 95% CI: 1.4, 7.7).5

These associations observed in the studies on famine cohorts suggest that nutritional deprivation in early life may damage kidney development and compromise renal function in adults, similarly to what has been observed in experiments with laboratory animals.7 In mice, the glomerular number was significantly less in protein-restricted offspring.34 In another study, pregnant rats fed a

Table 2. Famine exposure and levels of proteinuria in the rural sample (N = 51978)

<table>
<thead>
<tr>
<th>Reference group: unexposed cohort (1964–65)</th>
<th>OR (95% CI)</th>
<th>P-value</th>
<th>Adjusted OR 95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-famine cohort (1957–58)</td>
<td>1.29 (0.73, 2.26)</td>
<td>0.380</td>
<td>1.28 (0.73, 2.25)</td>
<td>0.366</td>
</tr>
<tr>
<td>Famine cohort (1959–61)</td>
<td>1.54* (1.04, 2.28)</td>
<td>0.029</td>
<td>1.53* (1.04, 2.26)</td>
<td>0.031</td>
</tr>
<tr>
<td>Post-famine cohort (1962–63)</td>
<td>1.26 (0.99, 1.59)</td>
<td>0.051</td>
<td>1.26 (0.99, 1.59)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

OR, odds ratio; adjusted OR, odds ratio estimated from models controlling for height, weight status, hypertension, occupation, education, month of birth and ethnicity.

*P-values are statistically significant at the 0.05 level.
low-protein diet produced offspring with reduced glomerulogenesis and, consequently, a lower nephron number. 35 Micronutrient deficiencies can also impair kidney development, which has been demonstrated in a series of studies with rats.36–39

We speculate that the elevated risk of proteinuria observed among Chinese women conceived during the famine was related to the impaired nephrogenesis that resulted from the famine exposure. In the human fetus, nephron formation starts around the 4th to 5th week of gestation and finishes around the 34th to 36th week of gestation.40 The number of nephrons increases slowly between the 10th and the 18th week, and then increases sharply from the 18th to the 32nd week.41 Once complete, nephrons and glomeruli cannot be formed later in life.41 Given that the nephrogenesis takes place before term birth, prenatal nutrient intake is likely important in determining the nephron endowment with which an individual is born and has for his/her lifetime.33,42,43 Stereological studies have suggested a direct relationship between the total glomerular number in the kidneys of adults and their birthweight, with an increase of 257 426 glomeruli associated with each 1-kg increase in birthweight.44 In turn, the glomerular filtration surface area remained low in people with less glomeruli,44–47 thereby increasing the risk of glomerular hyperfiltration and hypertension in remnant nephrons.42 Subsequent effects include glomerular injury with the onset of proteinuria, systemic hypertension and glomerulosclerosis.6,42 In the long run, glomerulosclerosis would further decrease the number of nephrons, which would result in chronic kidney diseases.42

Alternative mechanisms beyond nutrition-induced effects, such as the toxic effects of food substitutes including bark and clay,48,49 may not be entirely excluded, though they are less likely to play a major role given the consistency of findings from famine studies across various contexts.48

The rural sample in our data exhibited lower levels of protein in urine compared with the urban sample despite...
the fact that rural residents born before or during the famine were more intensively exposed to the famine compared with their urban counterparts and the evidence that the famine exposure was associated with elevated levels of proteinuria. It is worth noting that the famine effect on proteinuria was small in terms of effect size. Other factors including hypertension, diabetes mellitus and obesity predict renal malfunction in adult Chinese populations, and the patterns of such risk factors play major roles in health disparities in chronic kidney disease across regions and populations in China. It is speculated that, although urban residents are less likely to have experienced nutritional deprivation in early life than rural residents, their greater risk of hypertension and diabetes and unhealthy behaviours (including sedentary lifestyle and high-fat diet) in adulthood may have led to higher levels of proteinuria being observed in the urban sample.

The present study is subject to several limitations. First, we relied on a dipstick test of urine specimens, which has been widely used in outpatient settings to semi-quantitatively measure urinary protein concentrations. A dipstick test preferentially detects albumin, is less sensitive to globulins and its accuracy is lower than that of other methods including the 24-h proteinuria and the urinary protein/creatinine ratio tests used in clinical settings. The prevalence of proteinuria in our data is similar to the dipstick urinalysis results from International Society of Nephrology screening programmes, which suggested a prevalence of 3% proteinuria (>1+) in the Chinese population. The reliability of the dipstick test was not assessed in our study, but false-negative rates of 8–18% and false-positive rates of 5% were reported in other populations in conditions where testers received minimal training in urinalysis.

Second, we assumed that the women in our sample were living in the same county when the data were collected in the early 1990s as they did when they were born three decades earlier. This assumption is likely valid for our rural sample because the China-U.S. Collaborative Project for Neural Tube Birth Defect Prevention recruited residents with local registration (Hukou) for the study. In rural areas, women could obtain a local registration for another county through marriage but cross-county marriages were rare in these regions in the early 1990s. Urban woman may have been more likely to acquire local registration in different counties through other channels including employment by government, state-owned or collectively owned enterprises, but our analysis on the 1990 Chinese Census data suggested that a very low percentage (<4%) of women within the age range of our study subjects in the sampled provinces moved out of their county of residence during the period from 1985 to 1990.

Third, our analysis may be subject to sample selection from different sources. One is related to the fact that age and marital status affected the eligibility of participation in the US-China Collaborative Project; as a result, older women were underrepresented and unmarried women were not included. However, the bias due to this type of sample selection is expected to be modest because our difference-in-difference model substantially cancelled out differences across cohorts. In addition, compared with the post-famine birth cohorts, the famine cohorts were more likely to be born to parents who were more fertile and healthier (fertility selection); infants who were healthier or had better genetic endowment were more likely to survive the famine (survival selection). Therefore, the famine cohorts may represent a more selective and robust population compared with post-famine cohorts, which may result in an underestimation of the effects of famine exposure on adult health outcomes. Future studies comparing siblings with different exposure statuses to the famine (exposed vs unexposed) would reduce the biases due to fertility selection and survival selection and would be warranted if the data were available.

Lastly, unlike the Dutch famine that had a shorter duration (5–6 months) and clear starting- and end-points that provided evidence for a linkage between the famine exposure at different stages of gestation and health outcomes in adults, the long and imprecise duration of the Chinese famine of 1959–61 did not permit us to isolate prenatal and postnatal exposures.

Despite these limitations, the present study, as the first one to examine the effects of the Chinese famine of 1959–61 on renal function, linked exposure to the famine during gestation and early postnatal life with a higher level of proteinuria three decades later after the exposure in rural residents. Findings from our study and others suggest that undernutrition during critical early periods of life may hamper optimal development of certain organs, permanently altering their function, and may lead to elevated risks of chronic disease development. Such effect on a single chronic disease may be small in terms of effect size and may not be significant for individuals from a clinical point of view; however, the long-term effect of nutritional deprivation in critical early periods of life can be consequential for consideration at the population level. The impact of severe malnutrition in the first 1000 days of life (pregnancy and the first 2 years) on chronic illness as a whole therefore merits further investigation.

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References