Effects of stunting, diarrhoeal disease, and parasitic infection during infancy on cognition in late childhood: a follow-up study

Douglas S Berkman, Andres G Lescano, Robert H Gilman, Sonia L Lopez, Maureen M Black

Summary

Background Chronic malnutrition during infancy, marked by stunting, has been associated with poor cognitive function. We assessed the effect of stunting, diarrhoeal disease, and parasitic infections during infancy on cognitive function in late childhood.

Methods We followed up from birth to 2 years, a cohort of 239 Peruvian children for anthropometrics, stool samples, and diarrhoeal status. At 9 years of age, we assessed cognitive function in 143 (69%) with the full-scale intelligence quotient of the Wechsler Intelligence Scale for Children-Revised (WISC-R).

Findings All findings were adjusted for socioeconomic status and schooling; in addition, findings related to diarrhoea prevalence, *Giardia lamblia*, and *Cryptosporidium parvum* were adjusted for severe stunting. During the first 2 years of life, 46 (32%) of 143 children were stunted. Children with severe stunting in the second year of life scored 10 points lower on the WISC-R test (95% CI 2·4–17·5) than children without severe stunting. Children with more than one episode of *G lamblia* per year scored 4·1 points (0·2–8·0) lower than children with one episode or fewer per year. Neither diarrhoea prevalence nor *C parvum* infection was associated with WISC-R scores.

Interpretation Malnutrition in early childhood, indexed by stunting, and potentially *G lamblia*, are associated with poor cognitive function at age 9 years. If the observed associations are causal, then intervention programmes designed to prevent malnutrition and *G lamblia* early in life could lead to significant improvement in cognitive function of children in similar lower-income communities throughout the less-developed world.

* Lancet 2002; 359: 564–71
  See Commentary page 542

Introduction

Cognitive function in children is affected by environmental and health-related factors. Risk factors that interfere with cognitive function are especially important during infancy because the first 2 years of life are an essential period of rapid growth and development.

Diarrhoea is both a cause and an effect of malnutrition, and can lead to linear growth retardation. *Cryptosporidium parvum* and *Giardia lamblia*, two common enteric infections often associated with diarrhoea, adversely affect growth and nutritional status, especially during infancy. Research on the relation between cognitive function in children and diarrhoeal disease during infancy is limited. Guerra and colleagues noted that diarrhoea during infancy was negatively correlated with tests of cognitive function in Brazilian children. However, in this study, neither environmental nor health-related factors were considered, thus raising the possibility that the associations seen could be attributed to confounding.

The complex interrelations among malnutrition, diarrhoeal disease, and environmental factors such as socioeconomic status and education, make it difficult to determine the unique contribution of either malnutrition or diarrhoeal disease to cognitive development. For instance, because diarrhoeal disease can result in retarded growth, stunting becomes a potential confounder in the relation between diarrhoea and cognitive function.

We aimed to examine the associations between health-related factors during infancy and cognitive function in late childhood. First, we extended previous research that has linked stunting during infancy with poor cognitive function in late childhood by investigating multiple classifications of stunting and using a comprehensive, standardised, and widely accepted measure of cognitive function. Second, we assessed the independent effects of diarrhoeal disease, and *C parvum* and *G lamblia* infections during infancy on cognitive test scores in late childhood, after adjusting for stunting, schooling, and socioeconomic factors. If diarrhoeal disease during infancy is associated with cognitive function at 9-years-old after controlling for nutritional and environmental factors, our understanding of the long-term burden associated with diarrhoea and the health-related determinants of cognitive function will be greatly improved.

Patients and methods

Study setting

This study is a follow-up assessment of a cohort of children who were examined longitudinally from 1989–91. The study was done in Pampas de San Juan de Miraflores, a periurban shanty town in the outskirts of Lima, Peru. In 1989, most families in this community lived in houses constructed from woven thatch supported
by wooden poles. Less than a half of families had latrines or sewage connections, and water was largely supplied by municipal trucks and stored in cisterns or barrels that often became contaminated with faecal matter.11 Previous studies11,12,13 have described the community in more detail. Over the past decade, the population has grown to 40 000 people and the emigration rate has decreased. Today, most homes are constructed at least partly from brick, and have piped water and basic plumbing. Families in the community are similar in socioeconomic status, housing quality, and access to public utilities.11 A survey in 2000 reported a median income for heads of households of US$2100 per year (range $850–$4600; unpublished data).

**Enrolment**

Between September, 1989, and March, 1991, 253 mothers in their final trimester of pregnancy were randomly selected from the censused community and asked to participate in a study to describe the effect of *C parvum* infection on nutritional status.12 13 mothers declined, and one child died of pneumonia early in the study.12 The remaining 239 children (94%) were followed up prospectively from birth until November, 1991, for anthropometry and diarrhoeal illness. Cens

...
the child on a daily basis during infancy (mother, father, sibling, grandparent, or other relative) and whether the father lived in the home during this period.

Standardised height-for-age and weight-for-height Z scores were calculated with the EPINUT program in EpiInfo (version 6.04b). We defined stunting as an height-for-age Z score of less than −2; wasting was defined as weight-for-height Z score of less than −2, on the basis of WHO reference data.

We assessed age of the first stunting event by 6-month intervals (0–5, 6–11, 12–17, 18–24 months). Severity of stunting was classified as moderate (−3 ≤ height-for-age ≤ −2) and severe (height-for-age ≤ −3). Persistence of stunting was defined as persistent (stunted at least once during infancy and also in late childhood), catch-up (stunted at least once during infancy but not in late childhood), late incident (stunted for the first time in late childhood), and never stunted. We calculated stunting prevalence as the number of anthropometric measurements classified as stunted divided by the total number of measurements. This prevalence rate can be interpreted as the number of months stunted per year.

Wasting was assessed as both a continuous and dichotomous variable. Age at first wasting and wasting prevalence were also calculated. These expressions were then analysed by age intervals, but no associations with WISC-R scores were recorded.

A day of diarrhoea was defined as one in which a child passed three or more liquid or semi-liquid stools. Diarrhoea episodes were defined as at least 1 day of diarrhoea followed by 2 or more diarrhoea-free days. Diarrhoea incidence rates were calculated as the number of diarrhoea episodes by the total number of diarrhoea-free days. We calculated a diarrhoea prevalence rate by dividing the number of diarrhoea-positive days by the total number of days under surveillance for diarrhoea. Episodes of *C parvum* and *G lamblia* were defined as having one positive stool sample followed by at least three consecutive negative samples. Incidence rates for *C parvum* and *G lamblia* were calculated as the number of episodes divided by the number of stool samples at risk of a new episode (ie, total episode-free samples). We multiplied incidence by 52 to express it in episodes per year at risk, given that the number of stool samples assessed per year was 52 due to weekly collections. *C parvum* and *G lamblia* prevalence rates were calculated by dividing the number of positive weekly stool samples by the total number of stool samples. Episodes of *C parvum* and *G lamblia* were judged symptomatic if the child had at least one diarrhoea-positive day in the period 2 weeks before the beginning and 2 weeks after the end of the episode. Since giardia infections are commonly symptomless and can last for several weeks or even months, we also defined giardia-positive stools as symptomatic if the child had diarrhoea on any one of the 3 days surrounding or including the day the sample was collected. Thus, giardia-positive stools were also defined as asymptomatic in the absence of diarrhoea. We then calculated incidence and prevalence rates for symptomatic *C parvum* and both definitions of *G lamblia* infection by the same methods described previously. We estimated the median age at onset of first infection with the Kaplan-Meier statistic.

**Statistical analysis**

We used Stata (version 6.0) for all analyses, and one-way analysis of variance (ANOVA) for univariate analysis of the WISC-R scores. Sequential multivariate ANOVA was applied to identify factors independently associated with cognitive test scores; significance of the contribution of each variable was assessed with the F test after adjustment for the effects of variables already included in the model. We used the Wald test for the comparison of WISC-R scores for categorical variables with more than two categories. Regression coefficients were used to estimate the change in WISC-R scores between levels for categorical variables and for a one unit increase in continuous variables. We constructed multivariate models to adjust for the effects of socioeconomic status and education on cognitive test scores. Adjustment variables were selected by sequentially adding significant predictors from the univariate analysis into the model. We manually rotated the order of the variables to identify interactions and collinearity.

Continuous variables were truncated into fixed-size intervals and analysed as categorical variables to identify non-linear associations. If a monotonic trend or U-shaped relation was recorded between WISC-R scores and a particular covariate, an attempt was then made to combine categories that had similar WISC-R average scores.

Several variables were highly correlated and represented similar domains relating to cognitive function (eg, maternal and paternal education; school type and class size). In these cases, we chose the variable that explained the largest percentage of the variance and enhanced the strength of associations of the other variables in the model.

The presence of interactions in the final model was tested by introducing products of the variables by pairs into the model. The internal validity of our results was assessed by repeating the analyses on children who had more than 12 months of prospective surveillance from birth (ie, children who were followed up into the second year of life). The three exposure variables were also analysed by age categories in 6-month intervals (0–5, 6–11, 12–17, 18–24 months). This analytical strategy enabled us to identify effects that acted only during specific periods in infancy, and to further reduce the risk of misclassification that could arise when comparing children who were followed up prospectively for different lengths of time.

**Role of the funding source**

The study sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

**Results**

**Description of the sample**

Table 1 shows the characteristics of the children. All children were enrolled in school from grade 2 to 5. 25 (18%) of 141 children had been held back in school once and required to repeat a grade; nine (6%) had been held back at least twice (table 2). 46 (32%) of 143 children were stunted at least once during infancy. Of these, ten (22%) were severely stunted. Most stunted children became stunted between 6 and 17 months of age. Nearly half of children who were stunted during infancy had persistent stunting into late childhood; the remaining stunted children had catch-up growth and were not stunted at 9 years of age. Several expressions of stunting were correlated with each other. 146 (95%) of 151 persistently stunted children were stunted for the first time between 6 and 17 months of age whereas only 18 (68%) of 27 catch-up children were stunted for the first time during this period (p=0.02, χ² test). Catch-up children were nearly seven times as likely to be stunted at 9 years of age. 6–11, 12–17, 18–24 months). This analytical strategy enabled us to identify effects that acted only during specific periods in infancy, and to further reduce the risk of misclassification that could arise when comparing children who were followed up prospectively for different lengths of time.

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Table 1: Children’s characteristics

<table>
<thead>
<tr>
<th>Demographic characteristics</th>
<th>Children (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>9-36 (0-46)</td>
</tr>
<tr>
<td>Male sex</td>
<td>76 (53%)</td>
</tr>
<tr>
<td>WISC-R test scores*</td>
<td>88-9 (12-53)</td>
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</table>

<table>
<thead>
<tr>
<th>Stunting severity</th>
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<tbody>
<tr>
<td>Severe (HAZ &lt;–3)</td>
<td>10 (7%)</td>
</tr>
<tr>
<td>Moderate (–3 &lt; HAZ &lt; –2)</td>
<td>36 (25%)</td>
</tr>
<tr>
<td>Never stunted</td>
<td>97 (68%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diarrhoea episodes (total)</th>
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<tbody>
<tr>
<td>0-2</td>
<td>29 (20%)</td>
</tr>
<tr>
<td>3-4</td>
<td>35 (25%)</td>
</tr>
<tr>
<td>5-6</td>
<td>35 (25%)</td>
</tr>
<tr>
<td>7-8</td>
<td>23 (16%)</td>
</tr>
<tr>
<td>≥9</td>
<td>21 (14%)</td>
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<table>
<thead>
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<th>Diarrhoea prevalence (days/month) by age (months)*</th>
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<tr>
<td>0-5</td>
<td>3-60 (3-70)</td>
</tr>
<tr>
<td>6-11</td>
<td>2-06 (3-24)</td>
</tr>
<tr>
<td>12-17</td>
<td>1-67 (1-90)</td>
</tr>
<tr>
<td>18-24</td>
<td>1-70 (1-90)</td>
</tr>
<tr>
<td>0-11</td>
<td>2-93 (2-73)</td>
</tr>
<tr>
<td>≥12</td>
<td>1-67 (1-95)</td>
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<tr>
<th>Giardia episodes (total)</th>
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<tr>
<td>0</td>
<td>20 (14%)</td>
</tr>
<tr>
<td>1</td>
<td>37 (26%)</td>
</tr>
<tr>
<td>2</td>
<td>37 (26%)</td>
</tr>
<tr>
<td>3</td>
<td>28 (20%)</td>
</tr>
<tr>
<td>4</td>
<td>12 (8%)</td>
</tr>
<tr>
<td>5-7</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cryptosporidium episodes (total)</th>
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<tr>
<td>0</td>
<td>66 (46%)</td>
</tr>
<tr>
<td>1</td>
<td>47 (33%)</td>
</tr>
<tr>
<td>2</td>
<td>20 (14%)</td>
</tr>
<tr>
<td>3</td>
<td>10 (7%)</td>
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<table>
<thead>
<tr>
<th>Follow-up time (months)</th>
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<tr>
<td>6-11</td>
<td>28 (20%)</td>
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<tr>
<td>12-17</td>
<td>50 (35%)</td>
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<tr>
<td>18-23</td>
<td>43 (30%)</td>
</tr>
<tr>
<td>≥24</td>
<td>22 (15%)</td>
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Table 2: Association between education and socioeconomic factors and WISC-R test scores*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>b [95% CI]</th>
<th>p†</th>
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<tr>
<td>Grade</td>
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<tr>
<td>Fifth</td>
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<td>&gt;0-001</td>
</tr>
<tr>
<td>Second</td>
<td>7</td>
<td>-23-5 (-32-9 to –14-2)</td>
<td>&gt;0-001‡</td>
</tr>
<tr>
<td>Third</td>
<td>29</td>
<td>-11-7 (-17-5 to –6-0)</td>
<td>&gt;0-001‡</td>
</tr>
<tr>
<td>Fourth</td>
<td>76</td>
<td>-3-9 (-8-6 to 0-9)</td>
<td>0-110‡</td>
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<tr>
<td>School type</td>
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<td>115</td>
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<td>&lt;0-001</td>
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<tr>
<td>Private</td>
<td>26</td>
<td>10-3 (5-2 to 15-4)</td>
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<td>Class size</td>
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<tr>
<td>≥30</td>
<td>119</td>
<td>...</td>
<td>0-033</td>
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<tr>
<td>&lt;30</td>
<td>22</td>
<td>6-2 (0-5 to 11-8)</td>
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<td>Held back</td>
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<tr>
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<td>&gt;0-001</td>
</tr>
<tr>
<td>Yes</td>
<td>34</td>
<td>-12-4 (-16-8 to –8-0)</td>
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<td>Homework habits</td>
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<td>Always or almost always</td>
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<tr>
<td>Sometimes or never</td>
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<td>-10-2 (-16-4 to –4-1)</td>
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<td>Maternal education</td>
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<tr>
<td>No college-level education</td>
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<td>0-026</td>
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<tr>
<td>Some college schooling</td>
<td>6</td>
<td>11-5 (1-37 to 21-7)</td>
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<tr>
<td>Paternal education</td>
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<td></td>
<td></td>
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<tr>
<td>No college-level education</td>
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<td>...</td>
<td>&gt;0-001</td>
</tr>
<tr>
<td>Some college schooling</td>
<td>8</td>
<td>15-4 (6-8 to 24-1)</td>
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<td>Parity</td>
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<tr>
<td>1–3</td>
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<td>Father or mother</td>
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<td>...</td>
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<tr>
<td>Career</td>
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<td>Other§</td>
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<td>0-036</td>
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<tr>
<td>Technical employee</td>
<td>13</td>
<td>7-7 (0-5 to 14-8)</td>
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<tr>
<td>Floor type</td>
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<tr>
<td>Cement</td>
<td>119</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Soil</td>
<td>24</td>
<td>-8-6 (-14-0 to –3-2)</td>
<td>&lt;0-002</td>
</tr>
</tbody>
</table>

*Socioeconomic and education variables except for grade level and floor type, were determined from survey, which was completed in 141 children. |From ANOVA F test. †Wald test. ‡Three patients did not report a main source of household income.

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up and late incident children did not significantly differ from those who were never stunted. Children who were severely stunted had lower WISC-R scores compared with moderately stunted and non-stunted children (table 3). Children who were severely stunted in the second year of life scored much lower on the WISC-R test than children moderately stunted and non-stunted during that period.

Diarrhoea prevalence in the second year of life was significantly associated with cognitive test scores at age 9 (table 3). Between 12 and 24 months, a 1-day increase in diarrhoea per month was associated with a decrease in WISC-R scores.

G lamblia incidence was significantly associated with cognitive test scores (table 3). Children with more than 1 episode per year at risk had lower WISC-R test scores than children with one or fewer G lamblia episodes per year at risk. Neither symptomatic nor symptomless episodes and stool samples were associated with WISC-R scores. No associations were recorded between C parvum infection and cognitive test scores according to the number of episodes, incidence and prevalence, and symptomatic infections.

Multivariate-adjusted models

Class size and homework habits were no longer significant predictors of cognitive test scores after adjustment for school type, grade repetition, and grade level. In addition, maternal birthplace, level of education, parity, main source of income, career type, floor type, and language spoken at home while the child was learning to speak, were all accounted for by paternal education. We believe that paternal education had a stronger association with cognitive test scores because it is the most comprehensive indicator of household socioeconomic status in this community. Fathers were more likely to achieve higher educational levels than their wives or partners and were generally the main source of income in the household. These patriarchal patterns are common in Peru and many less-developed countries. Although conceptually each variable may have a specific effect, statistically they are all highly correlated. Paternal education was the only predictor that was independently associated with cognitive test scores after adjustment for maternal education and birthplace, parity, principal source of income and career type, floor type, and language spoken at home while the child was learning to speak.

Multivariate models for stunting were adjusted for four significant covariates: paternal education, school type, grade retention, and grade level. The models for diarrhoea prevalence and G lamblia incidence were also adjusted for severity of stunting in the second year of life. After multivariate adjustment, stunting prevalence and grade at first stunting event were still significant predictors of cognitive test score, whereas persistent stunting was no longer significant in multivariate analysis. Adjustment only modified slightly the effect of severe stunting in the

### Table 3: Relations of stunting, diarrhoeal disease and G lamblia infection to WISC-R test scores

<table>
<thead>
<tr>
<th>Stunting prevalence (months per year)</th>
<th>Children (n=143)</th>
<th>Unadjusted</th>
<th>Multivariate adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β (95% CI)</td>
<td>p†</td>
</tr>
<tr>
<td>&lt;2</td>
<td>143</td>
<td>-1·2 (-2·0 to -0·4)</td>
<td>0·005</td>
</tr>
<tr>
<td>≥2</td>
<td>38</td>
<td>Reference</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Age at first stunting event (months)</th>
<th>Stunting prevalence</th>
<th>Unadjusted</th>
<th>Multivariate adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β (95% CI)</td>
<td>p†</td>
</tr>
</tbody>
</table>
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Multivariate-adjusted models

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This figure is similar to the results reported by Mendez
life explained 4% of the variance in cognitive test scores.

and extends our conclusions to a wider range of
ability, greatly increases the internal validity of our results
widely used, comprehensive, and reliable test of cognitive
be established. Our use of the full-scale WISC-R, a
significant interactions were seen between any variables
WISC-R scores in a model including both severe stunting
after controlling for socioeconomic status, schooling, and
with WISC-R scores in the multivariate adjusted model
significant factors. Previous studies have been limited by
after adjustment for socioeconomic, schooling, and other
disappeared after adjustment for paternal education,
whilst the effect of stunting remained significant.
Because stunting and paternal education are both
ed significantly associated with WISC-R scores, and
stunting is not a unique consequence of diarrhoea, they
act as confounders by artificially creating the association
between diarrhoeal disease and cognitive test scores. The
effect of diarrhoeal disease on WISC-R was not found
Discussion
We have shown that stunting during infancy has a strong
adverse effect on cognitive function in late childhood. Severe stunting in the second year of life was associated with
a 10-point reduction in intelligence quotient scores
after adjustment for socioeconomic, schooling, and other
significant factors. Previous studies have been limited by
use of shorter, less comprehensive cognitive tests that are
restricted to specific domains of intellectual ability and
have relatively weak internal validity. Mendez and Adair\(^1\)
reported a similar association between severe stunting and cognitive function in Filipino children using a local
test of non-verbal intelligence. However, because the
construct validity of this test was not described, the
 correspondence of the reported differences in test scores
(1.4–3.3 points) with actual intelligence deficits cannot
be established. Our use of the full-scale WISC-R, a
widely used, comprehensive, and reliable test of cognitive
ability, greatly increases the internal validity of our results
and extends our conclusions to a wider range of
intellectual skills than those examined in other reports.

In our analysis, severe stunting in the second year of
life explained 4% of the variance in cognitive test scores.
This figure is similar to the results reported by Mendez
and Adair (3%–6%),\(^4\) despite the striking difference
between Peruvian and Filipino children in the proportion
of children who were severely stunted (22% vs 43%).
This finding shows that the negative effect of linear
growth retardation on cognitive function is not restricted
to settings with a high proportion of severely stunted
children.

Our results also show that prevalence and timing of the
first stunting event are related to a decrease in
intelligence quotient after adjustment for other significant
covariates. Sample size prevented us from examining the
independence of these effects from those of severe
stunting. However, if independent effects of stunting
severity, timing, and persistence on cognitive ability are
shown, then the burden of growth retardation will reach
even greater levels.

We did not assess iron status in this study. Surveillance
studies\(^26\) in this community and other shanty towns in
Lima have reported that about 25% of children under
4 years of age were anaemic. Since iron deficiency is a
risk factor for cognitive deficits in school-aged children,\(^27\)
we cannot rule out the possible effects of iron deficiency
on WISC-R scores.

In univariate analysis, diarrhoea prevalence in the
second year of life was associated with lower cognitive
test scores. Although children with higher diarrhoea
prevalence rates were more likely to be severely stunted
in the second year of life and have parents who were not
college educated (p < 0.001 and p = 0.008, likelihood-ratio test).

*G* *lamblia* incidence remained significantly associated
with WISC-R scores in the multivariate adjusted model
after controlling for socioeconomic status, schooling, and
severe stunting.

We were able to explain 40% of the variability in
WISC-R scores in a model including both severe stunting
in the second year of life and *Giardia* incidence, as well as
socioeconomic and schooling variables (figure). No
significant interactions were seen between any variables
in our multivariate-adjusted models.

**Factors associated with WISC-R test scores**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental education</td>
<td>-20</td>
</tr>
<tr>
<td>School type</td>
<td>-15</td>
</tr>
<tr>
<td>School retention</td>
<td>-10</td>
</tr>
<tr>
<td>School grade</td>
<td>-5</td>
</tr>
<tr>
<td>Severe stunting</td>
<td>0</td>
</tr>
<tr>
<td>Giardia incidence</td>
<td>5</td>
</tr>
<tr>
<td>G. lamblia</td>
<td>10</td>
</tr>
</tbody>
</table>

CIs are the change in mean WISC-R test scores associated with
the presence of each variable. Values at the right of the graph are the
percentage of the variance explained by each factor.
cognitive dysfunction. Other studies29,30 have recorded an association between cognitive function and helminth infections such as hookworm and Trichuris trichiura. However, the dry desert conditions present in the Pampas surrounding Lima are not conducive to survival, or transmission of geohelminths. Current data suggest a low prevalence from 0 to 0.8% of geohelminths such as Ascaris lumbricoides, T. trichiura, hookworm, and Strongyloides stercoralis in the Pampas, and that when infections do arise, severity is minimum.

We have reported a small effect of incident giardiasis on WISC-R test scores. The effect of giardiasis on WISC-R scores remained significant after adjustment for paternal education, schooling factors, and severe stunting, reducing the chance that residual confounding could explain these findings. Giardia infections reflect the occurrence of only a few specific events of faecal-oral contamination, making diarrhoeal disease a more comprehensive indicator of environmental contamination. However, in this study, WISC-R scores were associated with giardiasis and not with diarrhoeal disease, suggesting that G lamblia infection could be a better indicator of those aspects of environmental contamination that are associated with deficits in cognitive function. There is no evidence or rationale for a specific aspect of the pathogenesis of G lamblia infection to have deleterious effects on cognitive development. Nevertheless, giardiasis can lead to zinc and other micronutrient deficiencies that have been associated with deficits in cognitive development.31 Nash and Mowatt27 reported that G lamblia variant specific surface proteins bind zinc and other heavy metals in the intestine. Giardia can also cause malabsorption of fats.28

To keep the risks of confounding to a minimum, we modelled the effects of each variable significantly associated with WISC-R scores. Analysis of multiple expressions of each variable, excluding those that were colinear or redundant in their relation with cognitive test scores in univariate analyses, were made. This analytical strategy enabled us to obtain a highly parsimonious ANOVA model that explained 40% of the variance in WISC-R scores. Mendez and Adair reported very similar results using at least ten more variables and a sample size 15 times greater than ours. Our results show that a reduced set of carefully selected variables can appropriately describe the sources of variability in cognitive test scores and represent the most relevant domains affecting intelligence.

The combined effects of stunting and giardiasis account for an intelligence quotient deficit of almost 15 points. These results are important for re-evaluating the current estimates of the burden imposed by symptomatic and asymptomatic infections and malnutrition during infancy. Our finding of an association between giardia infections and decreased WISC-R scores is interesting and deserves further attention in a more rigorous study designed to account for multiple parasitic, bacterial, and viral enteric infections. Because of the high prevalence of stunting in children living in less-developed countries, estimated to be as high as 40% in children younger than 5 years of age,32 our results can be used in design of intervention programmes seeking to have the greatest effect on the adverse effects of stunting.

In our study, children who were severely stunted in the second year of life had the most substantial impairments in cognitive function. We also showed that children who had persistent stunting into late childhood were considerably more likely to be stunted for the first time after age 6 months and before 17 months compared with children who experienced catch-up growth. Children who either recovered early or became stunted late in infancy were relatively unaffected. Our results suggest that strategies to promote the cognitive function of school age children in less-developed countries should focus on securing the nutrition and wellbeing of children early in life.

Contributors
D Berkman designed the research methods, gathered data, managed data entry, devised the analytical framework for the study, did the statistical analysis, and wrote and edited the paper. A Lessan assisted in devising the analytical framework for the study and doing the statistical analysis, wrote most of the statistical analysis, and edited the paper. R Gilman participated in study design, advised in data collection, guided the scientific process, contributed to writing and editing of the paper, provided advice on the epidemiology of diarrhoeal diseases and G lamblia infection, and assisted with funding. S Lopez organised, managed, and did most of the data collection. M Black participated in study design, guided the scientific process, contributed to writing and editing of the paper, and provided advice on anthropometrics, and the assessment and interpretation of cognitive performance in children.

Conflict of interest statement
None declared.

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24 Martin Barratt

Uses of error

Assumptions

A Commentary on our trial comparing medical or 
surgical treatment for children with vesicoureteric reflux (VUR) and 
nephropathy picked up on a statement which was not strictly accurate. “We have shown that there are 
no differences in the outcome of children with severe VUR using medical or surgical management strategies”. 
It would have been more correct to say that we failed to 
demonstrate a significant difference in outcome between 
the two groups, but that if there were a benefit from 
surgery, we could be 95% confident that it was not more 
than 20% at 4 years, and 30% at 10 years of follow-up. 
We could well have missed a benefit from surgery, 
though it would be unethical. There was uncertainty about 
how long treatment with high dose steroids should 
continue after remission. I wanted to minimise steroid 
side effects and advocated withdrawal as soon as the urine 
was free of protein. This policy was the basis of our local 
management protocol, and was repeated in lectures, 
reviews, textbooks and consensus statements. However, 
others believed that longer courses of steroids were 
needed to prevent relapse, and in the end, several 
controlled trials proved them to be correct. Our desire to 
protect children from the side effects of prolonged 
treatment resulted in a higher relapse rate and more 
steroids in the long run. The mistake was not to have 
recognised earlier that a controlled trial would have 
resolved this dilemma.

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