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ORIGINAL ARTICLE

Infectious morbidity and white blood cell count associated with grade repetition and school absenteeism

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Abstract

Aim: Infections can impair cognitive development, but their role on adverse childhood educational outcomes is unknown. We examined the associations of infectious morbidity and inflammatory biomarkers with grade repetition and school absenteeism.

Methods: We followed 2762 Colombian children aged 5–12 years for a school year. We quantified inflammatory biomarkers at enrolment and prospectively recorded incidence of gastrointestinal and respiratory infections, doctor visits and absent days from school using pictorial diaries. We estimated adjusted relative risks (ARR) with 95% confidence intervals (CI) for grade repetition and absenteeism by infectious morbidity burden and inflammatory biomarker categories, and percentages of the associations mediated through absenteeism.

Results: Morbidity was associated with increased risk of grade repetition. ARR (95% CI) of grade repetition comparing high versus no incidence of gastrointestinal, respiratory and ear infections were, respectively, 2.17 (1.00, 4.72), 2.31 (1.28, 4.16) and 2.57 (1.13, 5.86). Infections also predicted school absenteeism, which mediated 35%, 31% and 38% of the corresponding morbidity-grade repetition associations. Elevated white blood cells (WBC), especially granulocytes, were related to increased grade repetition and school absenteeism risks.

Conclusion: Childhood infections and elevated WBC are associated with grade repetition and school absenteeism. Absenteeism does not fully explain the morbidity-grade repetition associations.

KEYWORDS
childhood infections, gastrointestinal morbidity, grade repetition, grade retention, granulocytes, respiratory infection, school absenteeism, white blood cells

Abbreviations: ARR, adjusted relative risk; CI, confidence interval; CRP, C-reactive protein; IQR, interquartile range; SES, socioeconomic status; USDA, United States Department of Agriculture; WBC, white blood cells.

1 | INTRODUCTION

Adverse academic outcomes among schoolchildren, including grade repetition and absenteeism, are widespread worldwide. Every year, 12% of students repeat a grade, on average.[1] Grade repetition and absenteeism predict low educational attainment, a strong risk factor for poor health and mortality in adulthood.[2]

Risk factors for grade repetition include material deprivation, nutritional deficiencies, lower birth order and absenteeism especially from sickness[3]; yet, the role of common infectious morbidity on grade repetition is virtually unknown. Infections could lead to grade repetition through impaired cognitive development. For example, gastrointestinal[4] and helminthic infections in infancy[5] or school age,[6] and malaria[7] have been related to measures of learning, memory and attention. Alternatively, infections could cause grade repetition through missing school days. Ascertaining if absenteeism mediates an association between infections and grade repetition could inform the extent to which a potential effect may be due to missing school versus infection-related brain development impairments; for example, through inflammation.

The aim of this study was to examine whether common respiratory and gastrointestinal infectious morbidity during a primary school year was associated with grade repetition. A secondary aim was to examine the relation between biomarkers of inflammation, which often results from recurrent infections, and grade repetition. We also examined whether infectious morbidity was related to school absenteeism, whether absenteeism was associated with grade repetition, and the extent to which absenteeism mediated the associations between infection and grade repetition.

Key Notes

- Whether common infections affect educational outcomes in school-age children is uncertain.
- Gastrointestinal and respiratory infections during a school year, and high white blood cell counts, increased risks of absenteeism and grade repetition in elementary school children from Bogotá, Colombia.
- Because only one-third of the association between infections and grade repetition was mediated through absenteeism, common infections might have a direct effect on neurocognitive function related to learning, possibly through inflammation.

2 | METHODS

2.1 | Study design and population

The study was conducted in the context of the Bogotá School Children Cohort, a longitudinal investigation of health and nutrition in Colombia. Details on the cohort design have been previously reported.[8] Briefly, in February 2006, we recruited 3202 children aged 5–12 years randomly selected from all 361 public primary schools in Bogotá. At the time of enrolment, we collected information on child, parental and household characteristics with the use of a parental self-administered survey. The questionnaire inquired about the child's health habits, maternal education, height and weight. Household food insecurity was assessed with a validated Spanish language version of the USDA Household Food Security Survey module, and household socioeconomic status (SES) was ascertained using the government classification system prevalent at the time. This system assigned each home address one of six ordinal rankings (1 representing the lowest SES) according to household income and material characteristics.

During the weeks following enrolment, trained research assistants visited participating children at their schools to obtain anthropometric measurements. Height was measured without shoes to the nearest 1 mm using a wall-mounted portable Seca 202 stadiometer (Seca, Hanover, MD). At the same visits, a fasting blood sample was obtained through antecubital venipuncture. The samples were protected from sunlight and transported in refrigerated coolers on the day of collection to the Colombian National Institute of Health.

Throughout the academic year following enrolment into the cohort, parents or primary caregivers kept daily records of morbidity episodes, doctor visits and days children were absent from school using a 7-day diary that was distributed and returned on a weekly basis. To record morbidity episodes, the diaries had drawings depicting children with symptoms including vomiting, diarrhoea, fever, cough and earache/discharge. Caregivers were asked to record the presence of these symptoms daily on check boxes. Diaries have been used to register participants' symptoms in studies of gastrointestinal and respiratory illness.[9] The use of symptom diaries has been validated to capture incidence of infectious morbidity.[10]

One year after enrolment, we collected information on grade repetition. According to the academic policy prevalent in Bogotá at the time, a child was retained in the same grade when they failed three subjects, two of which were math and language. We obtained public school listings of the next academic year from the Secretary of Education to ascertain the school year's outcome. If children appeared in the same grade as they were in the previous year, they were considered to have failed. We found 2589 children in these listings. For children who had left the public school system, we asked parents about the school year's outcome as part of a follow-up survey and obtained information in 245. Information was unavailable for 11% of cohort participants.

The parents or primary caregivers of all children gave written informed consent prior to enrolment in the study. The Ethics Committee of the National University of Colombia Medical School approved the study protocol; the University of Michigan Institutional Review Board approved the use of data from the study.

2.2 | Laboratory methods

All analyses took place at the Colombian National Institute of Health. We carried out a complete blood count in whole blood; serum C-reactive protein (CRP) concentration was measured using a turbidimetric immunoassay on an ACS180 analyser (Bayer Diagnostics, Tarrytown, NY). Vitamin B12 was quantified using a competitive chemiluminescent immunoassay in an ADVIA Centaur analyser (Bayer Diagnostics, Tarrytown, NY). Haemoglobin concentrations were quantified with a hemiglobincyanide method.

2.3 | Data analysis

Outcomes. The primary outcome of interest was grade repetition, based on public school listings or parental report. A secondary outcome was high absenteeism. Absenteeism was the proportion of days children were marked absent from school in the pictorial diaries out of the total number of observed days they should have attended, excluding weekends and holidays. One school year has about 200 days. High absenteeism was the fourth quartile among children with >0 missed days of school.

Exposures. The exposures of interest were (1) infectious morbidity during a school year and (2) biomarkers of inflammation at the time of recruitment including white blood cell (WBC), granulocyte and lymphocyte counts, and serum CRP concentrations.

Infectious morbidity exposures were defined using the parental report of symptoms on the pictorial diaries. We defined three syndromes to represent infectious morbidity by combining symptoms reported on the same day in the pictorial diaries: diarrhoea with vomiting, cough with fever and earache or ear discharge with fever. Diarrhoea with vomiting has been related to clinically diagnosed episodes of gastrointestinal illness.[11] Cough with fever had a positive predictive value of 83% for laboratory-confirmed influenza infection among children 5–12 years old,[12] and this case definition has been used in Latin America. Cough with fever is also reported in school-age children experiencing the common cold due to various viral and bacterial infections.[9] Although the diagnosis of acute otitis media requires clinical examination, symptoms including moderate-to-severe ear pain with fever are indicators of severe illness and ear drainage is often related to bacterial infection.[13] We also considered doctor visits on syndrome days as a severe infection surrogate. Because there is not a conventionally accepted categorisation of morbidity rates in middle childhood, we used the study population distributions to define morbidity levels as previously done in other populations.[14] Since a majority of children had no episodes, zero rates ('none') were the reference category for all infectious syndromes. Moderate and high annual syndrome rates were defined as values < versus ≥ the fourth quartile for children with non-zero rates.

WBC counts are an established biomarker for infection and inflammation in clinical practice; they have been used in the paediatric population to assess chronic inflammation,[15] which may result from frequent infections. Elevated WBC count was defined as values >12 000 and > 10 500/mm^3 for children < and ≥ 10 years of age, respectively.[16] Elevated granulocyte and lymphocyte count was defined as above their normal ranges[16]; >6500/mm^3 and > 3000/mm^3, respectively. CRP is a low cost, validated, frequently used biomarker of systemic inflammation. Elevated CRP was defined as >3.0 mg/L, which has been previously used to indicate low-grade systemic inflammation in children.[17]

Covariates. We considered as potential confounders variables that were independent predictors of grade repetition[18] and that could be associated with the exposures without being their consequences.[19] These included the child's sex, age at enrolment, height-for-age *Z*-score per the World Health Organisation reference, anaemia (haemoglobin <12.7 g/dL, an altitude-adjusted cut point), vitamin B12 deficiency (serum concentration < 148 pmol/L[20]), household food insecurity with hunger (≥13 affirmative responses to the survey's 16 questions on adverse experiences[21]) and SES (from 1 –lowest– to 4 in the sample).

Statistical analysis. Of the 2834 participating children with information on grade repetition, 72 lacked information on absenteeism and were excluded. Hence, the analytic sample comprised 2762 children.

We calculated risks of grade repetition and high absenteeism according to each infectious morbidity syndrome or inflammatory biomarker category. Next, we estimated adjusted relative risks and 95% confidence intervals (CIs) between exposure groups with use of Poisson regression models. Tests for linear trend were carried out by introducing into the models a variable representing ordinal categories of the exposure as a continuous covariate. All models specified robust variances and accounted for correlations between siblings.

To assess whether absenteeism mediated the associations between infectious morbidity or inflammatory biomarkers and grade repetition, we first quantified the association of high absenteeism with risk of grade repetition in this population, assuming that infections preceded absenteeism in time. Next, we implemented causal mediation analyses[22] under the assumptions of a counterfactual frame to estimate the proportion of any associations between infectious morbidity or inflammatory biomarker exposures (E) and the grade repetition outcome (O) that was mediated through high absenteeism (M). The assumptions involved lack of unmeasured confounding (common causes) in the E-O, M-O and E-M relations, and no effect of E on confounders of the M-O relation. All models included an E-M interaction term to allow estimation of natural direct E-O effects. All analyses were performed with use of the Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC).

3 | RESULTS

Mean ± SD children's age at baseline was 8.7 ± 1.8 years; 50.7% were girls. Children contributed 327 857 days of observation for infectious morbidity during the follow-up year (median per child, 126; IQR, 70, 168). Annual morbidity rates (days per child-year) of diarrhoea with vomiting, cough with fever and ear pain/ear discharge with fever were, respectively, 1.0, 3.0 and 0.8. The annual rate of doctor visits on days with symptoms was 0.6. Mean ± SD baseline WBC count

and CRP concentrations were, respectively, 7123 ± 2025/mm^3 and 1.4 ± 2.6 mg/L. Overall risk of grade repetition and high absenteeism was, respectively, 4.8% and 11.1%.

3.1 | Infectious morbidity during the school year

Grade repetition. Infectious morbidity was associated with an increased risk of grade repetition. Adjusted relative risks [ARR (95% CI)] of grade repetition for high versus no incidence of diarrhoea with vomiting, cough with fever, ear infections and doctor visits on days with symptoms were, respectively 2.17 (1.00, 4.72), 2.31 (1.28, 4.16), 2.57 (1.13, 5.86) and 3.80 (1.92, 7.50) (Table 1).

School absenteeism. Infectious morbidity and doctor visits on days with symptoms were strongly related to risk of high absenteeism. ARR (95% CI) of absenteeism for high versus no incidence of diarrhoea with vomiting, cough with fever, ear infections and doctor visits on days with symptoms were, respectively, 3.80

TABLE 1 Infectious morbidity syndromes in middle childhood and risk of grade repetition among elementary school children from Bogotá, Colombia.

Annual syndrome rates[a]	*n*	Grade repetition risk (%)	Relative risk (95% CI)[b]	
			Age and sex-adjusted	Multivariable-adjusted[c]
Diarrhoea with vomiting				
None	2400	4.6	1.00	1.00
Moderate	271	5.5	1.24 (0.74, 2.08)	1.22 (0.70, 2.12)
High	91	8.8	2.13 (1.07, 4.23)	2.17 (1.00, 4.72)
p, trend[d]		0.05	0.02	0.04
Cough with fever				
None	2035	4.5	1.00	1.00
Moderate	549	4.6	1.08 (0.71, 1.66)	1.24 (0.79, 1.95)
High	178	9.0	2.19 (1.29, 3.73)	2.31 (1.28, 4.16)
p, trend		0.02	0.005	0.005
Earache/discharge with fever				
None	2535	4.6	1.00	1.00
Moderate	170	6.5	1.51 (0.84,2.73)	1.50 (0.80, 2.79)
High	57	8.8	2.13 (0.91,5.01)	2.57 (1.13, 5.86)
p, trend		0.08	0.03	0.01
Doctor visits on syndrome days				
None	2554	4.8	1.00	1.00
Moderate	156	1.9	0.43 (0.14, 0.34)	0.50 (0.16, 1.55)
High	52	13.5	3.12 (1.55, 6.27)	3.80 (1.92, 7.50)
p, trend		0.04	0.02	0.002

[a]Moderate and high annual syndrome rates (days with syndrome per year) correspond to values < versus ≥ the fourth quartile for children with rates >0. The fourth quartile (days per year) is 8.7, 13.5, 9.5 and 6.8 for diarrhoea with vomiting, cough with fever, earache / discharge with fever and doctor visits on syndrome days, respectively.

[b]From Poisson regression models with grade repetition as the dichotomous outcome and indicator variables for each combination of symptoms as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.

[c]From Poisson regression models adjusted for child's sex, age, height-for-age Z-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. Complete case analysis, $n = 2330$.

[d]Wald test for a variable representing the median value of each ordinal category introduced into the linear regression model as a continuous predictor.

(2.70, 5.33), 4.57 (3.43, 6.08), 4.43 (3.09, 6.35) and 5.19 (3.73, 7.24) (Table 2).

Mediation of the infectious morbidity-grade repetition association through absenteeism. High absenteeism was associated with a 2.08-times (95% CI 1.32, 3.28) increased risk of grade repetition (Table 3). Absenteeism mediated 31%–38% of the associations between infectious morbidity syndromes and grade repetition (Table 4).

3.2 | Inflammatory biomarkers

Elevated WBC counts were related to a 2.81-times (95% CI 1.34, 5.90) higher risk of grade repetition, compared with normal counts (Table 5). This risk increase was due to elevated granulocytes. CRP was not associated with risk of grade repetition. Compared with normal counts, elevated WBC counts were associated with a 1.78-times (95% CI 1.04, 3.07) increased risk of high absenteeism (Table 6). CRP was not related to this outcome. Only 11% of the association between WBC counts and grade repetition was mediated through high absenteeism (Table 7).

4 | DISCUSSION

In this longitudinal investigation of Colombian schoolchildren, gastrointestinal and respiratory infectious morbidity and related doctor visits were associated with increased risks of grade repetition and school absenteeism. School absenteeism did not fully account for

TABLE 2 Infectious morbidity syndromes in middle childhood and risk of high absenteeism from school among elementary school children from Bogotá, Colombia.

Annual syndrome rates[a]	*n*	High absenteeism[b] risk (%)	Relative risk (95% CI)[c] Age and sex-adjusted	Relative risk (95% CI)[c] Multivariable-adjusted[d]
Diarrhoea with vomiting				
None	2400	9.8	1.00	1.00
Moderate	271	15.5	1.59 (1.17, 2.15)	1.59 (1.15, 2.19)
High	91	33.0	3.35 (2.44, 4.60)	3.80 (2.70, 5.33)
p, trend[e]		<0.0001	<0.0001	<0.0001
Cough with fever				
None	2035	7.9	1.00	1.00
Moderate	549	15.7	1.99 (1.56, 2.54)	2.02 (1.54, 2.64)
High	178	33.7	4.26 (3.29, 5.50)	4.57 (3.43, 6.08)
p, trend		<0.0001	<0.0001	<0.0001
Earache/discharge with fever				
None	2535	9.9	1.00	1.00
Moderate	170	18.8	1.90 (1.37, 2.65)	2.03 (1.44, 2.86)
High	57	38.6	3.91 (2.76, 5.53)	4.43 (3.09, 6.35)
p, trend		<0.0001	<0.0001	<0.0001
Doctor visits on syndrome days				
None	2554	9.4	1.00	1.00
Moderate	156	25.0	2.61 (1.94, 3.52)	2.69 (1.95, 3.71)
High	52	51.9	5.44 (4.07, 7.26)	5.19 (3.73, 7.24)
p, trend		<0.0001	<0.0001	<0.0001

[a]Moderate and high annual syndrome rates (days with syndrome per year) correspond to values < versus ≥ the fourth quartile for children with rates >0. The fourth quartile (days per year) is 8.7, 13.5, 9.5 and 6.8 for diarrhoea with vomiting, cough with fever, earache/discharge with fever and doctor visits on syndrome days, respectively.

[b]High absenteeism corresponds to values ≥ the fourth quartile for children with >0 missed days during the academic year. The fourth quartile (days per year) is 7.6.

[c]From Poisson regression models with high absenteeism as the dichotomous outcome and indicator variables for each combination of symptoms as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.

[d]From Poisson regression models adjusted for child's sex, age, height-for-age Z-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES.

[e]Wald test for a variable representing the median value of each ordinal category introduced into the linear regression model as a continuous predictor.

TABLE 3 School absenteeism and risk of grade repetition among elementary schoolchildren from Bogotá, Colombia.

Absenteeism[a]	*n*	Grade repetition risk (%)	Relative risk (95% CI)[b]	
			Age and sex-adjusted	Multivariable-adjusted[c]
Low	2456	4.4	1.00	1.00
High	306	8.5	1.99 (1.32, 3.01)	2.08 (1.32, 3.28)
p		0.002	0.001	0.002

[a]Low and high absenteeism corresponds to values < versus ≥ the fourth quartile for children with >0 missed days during the academic year. The fourth quartile (days per year) is 7.6.

[b]From Poisson regression models with grade repetition as the dichotomous outcome and absenteeism as the exposure. Robust estimates of variance were used in all models to account for correlations between siblings.

[c]From Poisson regression models adjusted for child's sex, age, height-for-age *Z*-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. Complete case analysis, $n = 2330$.

TABLE 4 Mediation of school absenteeism on the associations between infectious morbidity and grade repetition among elementary schoolchildren from Bogotá, Colombia.

Syndrome[a]	Morbidity-grade repetition association within levels of absenteeism[b]			Morbidity-grade repetition association			
	Adjusted relative risk (95% CI)		*P* for exposure-mediator interaction	Adjusted relative risk (95% CI)			
	Low	High		Total[c]	Direct	Indirect through high absenteeism	% mediated
Diarrhoea with vomiting	1.79 (0.60, 5.38)	1.68 (0.55, 5.15)	0.94	2.15 (0.94, 4.93)	1.74 (0.75, 4.04)	1.23 (1.03, 1.48)	35
Cough with fever	1.64 (0.67, 3.99)	2.12 (0.93, 4.86)	0.67	2.22 (1.23, 4.02)	1.84 (1.00, 3.38)	1.21 (1.02, 1.43)	31
Earache/discharge with fever	1.96 (0.52, 7.32)	1.93 (0.64, 5.80)	0.98	2.51 (1.01, 6.26)	1.94 (0.77, 4.91)	1.29 (1.03, 1.61)	38
Doctor visits on syndrome days	2.57 (0.73, 9.10)	3.28 (1.37, 7.88)	0.75	3.94 (1.80, 8.64)	3.01 (1.34, 6.77)	1.31 (1.02, 1.68)	32

[a]Annual syndrome rates (days with syndrome per year) ≥ the fourth quartile for children with rates >0. The fourth quartile is 8.7, 13.5, 9.5 and 6.8 for diarrhoea with vomiting, cough with fever, earache/discharge with fever and doctor visits on syndrome days, respectively.

[b]Low and high absenteeism corresponds to values < versus ≥ the fourth quartile for children with >0 missed days during the academic year. The fourth quartile (days per year) is 7.6.

[c]From Poisson regression models with grade repetition as the dichotomous outcome adjusted for child's sex, age, height-for-age *Z*-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. The association between each syndrome and absenteeism was modelled with use of logistic regression.

the associations between infectious morbidity and grade repetition. Elevated WBC count, an inflammatory biomarker, was also associated with increased risks of grade repetition and absenteeism.

One possible mechanism to explain the associations between infectious morbidity and grade repetition is an adverse effect of diarrheal[23] and respiratory[24] infections on neurocognitive development. Infection-induced inflammatory responses could mediate these effects. In the Avon Longitudinal Study of Parents and Children, high CRP, a marker of inflammation, was related to decreased IQ.[25] Cytokines produced in response to acute infections may traverse the blood–brain barrier from the periphery via active transport, diffusion from circumventricular organs or blood–brain barrier secretion.[26] In the brain, cytokines could disrupt microglia-mediated processes such as the survival, differentiation and maturation of neurons during neurogenesis as well as synaptic pruning. Additionally, proinflammatory cytokines may directly alter myelin structures or induce a cascade of immune responses that promote demyelination, affecting processing speed.[27] Although many neurodevelopmental events occur in utero and before 3 years of age, critical changes in synapse number and myelin integrity continue to occur in middle childhood.[28] Hence, this life stage remains an important developmental period in which infection and inflammation may shape subsequent neurodevelopment, cognition and academic performance.

Three findings in our study may lend indirect support to the notion that the association between infections and grade repetition is due to inflammation affecting the brain. First, although we lacked measures of inflammation during the gastrointestinal and respiratory infection episodes, we found that elevated WBC counts at recruitment predicted increased risk of grade repetition. WBC increases acutely in response to infections and children with elevated WBC may have had an asymptomatic infection on the day

TABLE 5 Inflammatory biomarkers in middle childhood and risk of grade repetition among elementary schoolchildren from Bogotá, Colombia.

Inflammatory biomarkers	*n*	Grade repetition risk (%)	Relative risk (95% CI)[a]	
			Age and sex-adjusted	Multivariable-adjusted[b]
White blood cell count[c]				
Not elevated	2394	4.7	1.00	1.00
Elevated	60	11.7	2.54 (1.25, 5.19)	2.81 (1.34, 5.90)
p		0.01	0.01	0.006
Granulocytes[d]				
Not elevated	2623	4.6	1.00	1.00
Elevated	139	9.4	2.10 (1.22, 3.63)	2.21 (1.23, 3.96)
p		0.01	0.008	0.008
Lymphocytes[e]				
Not elevated	1850	5.2	1.00	1.00
Elevated	912	4.1	0.86 (0.59, 1.25)	0.82 (0.54, 1.26)
p		0.20	0.43	0.37
C-reactive protein mg/L				
≤3 mg/L	2562	4.8	1.00	1.00
>3 mg/L	200	5.0	1.12 (0.60, 2.10)	1.01 (0.50, 2.05)
p		0.90	0.72	0.97

[a]From Poisson regression models with grade repetition as the dichotomous outcome and each inflammatory biomarker as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.

[b]From Poisson regression models adjusted for child's sex, age, height-for-age *Z*-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. Complete case analysis, $n = 2241$.

[c]Elevated white blood cell count corresponds to values >12 000 and > 10 500 /mm^3 for children < and ≥ 10 years of age, respectively.

[d]Elevated granulocytes are defined as >6500 /mm^3.

[e]Elevated lymphocytes are defined as >3000 /mm^3.

of assessment. However, high WBC could also represent low-grade chronic inflammation due to recurrent infections. Second, school absenteeism could have a deleterious effect on academic performance, independent of cognitive functioning; yet, absenteeism mediated only about one-third of the associations between infectious morbidity and grade repetition. Finally, syndromes representing infections of different systems and aetiologies were all related to grade repetition. Although diarrheal disease can be caused by a range of viral, bacterial or parasitic agents in children of this age, norovirus infection is a very common aetiology of diarrhoea and vomiting in school-age children[11] and could have underlain many of the episodes in our study. Cough with fever can be caused by viral or bacterial infections,[9] whereas ear infections are often bacterial in middle childhood.[13] While different aetiological agents elicit distinct immune responses, inflammation may be an underlying mechanism common to all.

In our study, absenteeism was not only a risk factor for academic failure but also mediated the association between infectious morbidity and grade repetition. This means that children who become ill and stay at home may miss critical learning opportunities that shape their academic performance. Increased awareness of the long-term impacts on learning of illness-related missed school days is needed. Interventions such as hand hygiene[29] could improve student attendance, but children who frequently miss school due to illness may require more substantial support to diminish the effects of absenteeism on academic performance.

This study has several strengths. It was conducted in a large and representative sample of Latin American schoolchildren, an understudied population. The longitudinal design limits the possibility of reverse causation bias. The prospective collection of infectious morbidity data also precludes misclassification due to recall bias. The use of pictorial symptom diaries to accurately capture incidence of infectious morbidity has been previously validated. We had an opportunity to control for relevant potential confounders of the associations between infectious morbidity, inflammation and grade repetition. Finally, the consistency of the associations with self-reported

TABLE 6 Inflammatory biomarkers in middle childhood and risk of high absenteeism from school among elementary schoolchildren from Bogotá, Colombia.

Inflammatory biomarkers	*n*	High absenteeism[a] risk (%)	Relative risk (95% CI)[b]	
			Age and sex-adjusted	Multivariable-adjusted[c]
White blood cell count[d]				
Not elevated	2394	10.9	1.00	1.00
Elevated	60	18.3	1.67 (0.98, 2.87)	1.78 (1.04, 3.07)
p		0.06	0.06	0.04
Granulocytes[e]				
Not elevated	2623	11.0	1.00	1.00
Elevated	139	13.7	1.23 (0.80, 1.88)	1.29 (0.83, 2.00)
p		0.31	0.35	0.26
Lymphocytes[f]				
Not elevated	1850	11.0	1.00	1.00
Elevated	912	11.2	0.97 (0.78, 1.22)	1.00 (0.78, 1.28)
p		0.90	0.82	0.99
C-reactive protein mg/L				
≤3 mg/L	2562	11.2	1.00	1.00
>3 mg/L	200	9.0	0.79 (0.50, 1.24)	0.84 (0.53, 1.33)
p		0.33	0.30	0.45

[a]High absenteeism corresponds to values ≥ the fourth quartile for children with >0 missed days during the academic year. The fourth quartile (days per year) is 7.6.

[b]From Poisson regression models with high absenteeism as the dichotomous outcome and each inflammatory biomarker as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.

[c]From Poisson regression models adjusted for child's sex, age, height-for-age Z-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. Complete case analysis, $n = 2241$.

[d]Elevated white blood cell count corresponds to values >12 000 /mm^3 and > 10 500/mm^3 for children < and ≥ 10 years of age, respectively.

[e]Elevated granulocytes are defined as >6500/mm^3.

[f]Elevated lymphocytes are defined as >3000/mm^3.

TABLE 7 Mediation of school absenteeism on the associations between inflammatory biomarkers and grade repetition among elementary schoolchildren from Bogotá, Colombia.

	Inflammatory biomarker-grade repetition association within levels of absenteeism[a]			Inflammatory biomarker-grade repetition association			
	Adjusted relative risk (95% CI)			Adjusted relative risk (95% CI)			
Inflammatory biomarker	Low	High	*P* for exposure-mediator interaction	Total[b]	Direct	Indirect through high absenteeism	% mediated
Elevated white blood cell count[c]	3.55 (1.63, 7.74)	0.89 (0.12, 6.83)	0.21	2.74 (1.26, 5.97)	2.54 (1.17, 5.53)	1.08 (0.97, 1.20)	11

[a]Low and high absenteeism corresponds to values < versus ≥ the fourth quartile for children with >0 missed days during the academic year. The fourth quartile (days per year) is 7.6.

[b]From Poisson regression models with grade repetition as the dichotomous outcome adjusted for child's sex, age, height-for-age Z-score, vitamin B12 deficiency, and anaemia, household food insecurity with hunger and SES. The association between elevated white blood cell count and absenteeism was modelled with use of logistic regression.

[c]Elevated white blood cell count corresponds to values >12 000 and > 10 500 /mm^3 for children < and ≥ 10 years of age, respectively.

morbidity and objectively determined inflammatory biomarkers increases the internal validity of the study.

Some limitations are also worth noting. In this observational study, causality cannot be inferred without strong assumptions, including absence of misclassification and selection biases and lack of unmeasured confounding. For example, we cannot rule out residual confounding by other relevant predictors of grade repetition such as underlying chronic disorders and more detailed measures of

SES. Since there are no agreed-upon categorisations of infectious morbidity in middle childhood, we grouped the burden of infection using the distribution of morbidity within our study population. This may limit the comparability of results between populations; however, some of the cut points used to define high rates of illness in this study seem consistent with those reported in others. For example, German schoolchildren had a mean 1.3 common cold episodes per year each lasting about one week[30]; our definition of high rates of cough with fever (≥13.5 days/year) would correspond to being above that mean. A single baseline measurement of inflammatory biomarkers may be subject to large within-person variation given that inflammation may increase acutely in response to an infectious episode. This may lead to random error and possibly an attenuation of the associations. The morbidity patterns observed during the study school year may be correlated with the morbidity burden in previous years. Therefore, the associations of morbidity with grade repetition may represent a cumulative effect of infections over multiple years rather than a short-term effect during the year of observation. We did not have access to the children's grades in specific subjects; this could have enhanced our understanding of the cognitive processes affected by infection. We lacked information on the microbial aetiology of the morbidities evaluated in the study. Finally, analyses were conducted several years after data collection due to funding constraints and it is possible that associations may have changed over time.

In conclusion, a high burden of common infections in middle childhood is associated with increased risks of grade repetition and school absenteeism. The association between infections and grade repetition might be partly due to an effect of neuroinflammation on cognitive performance. Intervention studies are warranted to elucidate whether reducing the burden of common infections and school absence improves educational outcomes among children.

AUTHOR CONTRIBUTIONS

Eduardo Villamor: Conceptualization; investigation; funding acquisition; writing – original draft; methodology; supervision; formal analysis. **Rachael J. Beer:** Writing – original draft; methodology; formal analysis. **Allison L. Seeley:** Writing – review and editing; investigation. **Sandra López-Arana:** Writing – review and editing; investigation. **Constanza Marín:** Data curation; project administration; writing – review and editing. **Mercedes Mora-Plazas:** Data curation; project administration; writing – review and editing; funding acquisition.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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