Development and Psychopathology (2023), **35**, 301–313
doi:10.1017/S0954579421000675

CAMBRIDGE UNIVERSITY PRESS

Regular Article

Common infectious morbidity and white blood cell count in middle childhood predict behavior problems in adolescence

Rachael J. Beer[1], Kallisse R. Dent[1], Sonia L. Robinson[2], Henry Oliveros[3], Mercedes Mora-Plazas[4], Constanza Marin[3] and Eduardo Villamor[1]

[1]Department of Epidemiology, University of Michigan School of Public Health, 1420 Washington Heights, Ann Arbor, MI 48109, USA; [2]*Eunice Kennedy Shriver* National Institute of Child Health and Development, Rockville, MD, USA; [3]Universidad de La Sabana, Chía, Colombia and [4]Foundation for Research in Nutrition and Health, Bogotá, Colombia

Abstract

We examined the associations of middle childhood infectious morbidity and inflammatory biomarkers with adolescent internalizing and externalizing behavior problems. We recruited 1018 Colombian schoolchildren aged 5–12 years into a cohort. We quantified white blood cell (WBC) counts and C-reactive protein at enrollment and prospectively recorded incidence of gastrointestinal, respiratory, and fever-associated morbidity during the first follow-up year. After a median 6 years, we assessed adolescent internalizing and externalizing behavior problems using child behavior checklist (CBCL) and youth self-report (YSR) questionnaires. Behavior problem scores were compared over biomarker and morbidity categories using mean differences and 95% confidence intervals (CI) from multivariable linear regression. Compared with children without symptoms, CBCL internalizing problem scores were an adjusted 2.5 (95% CI: 0.1, 4.9; $p = .04$) and 3.1 (95% CI: 1.1, 5.2; $p = .003$) units higher among children with moderate diarrhea with vomiting and high cough with fever rates, respectively. High cough with fever and high fever rates were associated with increased CBCL somatic complaints and anxious/depressed scores, respectively. WBC >10,000/mm^3 was associated with both internalizing problem and YSR withdrawn/depressed scores. There were no associations with externalizing behavior problems. Whether or not decreasing the burden of common infections results in improved neurobehavioral outcomes warrants further investigation.

Keywords: anxious/depressed behavior, diarrheal disease, internalizing behavior, respiratory infection, somatic complaints

(Received 5 February 2021; revised 1 June 2021; accepted 1 June 2021; First Published online 23 August 2021)

Mental health disorders affect approximately 13.4% of children and adolescents, and are associated with increased risk of adverse health outcomes in the short and long term (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015; Prince et al., 2007). Behavior problems are among the most common mental health complaints in youngsters; they are associated with premature death (von Stumm et al., 2011) and adult-life illness including depressive, anxiety, bipolar, obsessive-compulsive, and panic disorders (Roza, Hofstra, van der Ende, & Verhulst, 2003). Because most behavior disorders develop between 11 and 18 years of age (Patton et al., 2016), it is essential to understand their determinants at earlier ages.

Infection and the resulting inflammatory response may play an important role in neurobehavioral development and risk of mental illness. Acute infections trigger the immune system to release cytokines and chemokines which help to regulate the immune response. Cytokines can be released directly from neurons and glial cells within the central nervous system or may traverse the blood–brain barrier from the periphery via active transport, diffusion from circumventricular organs, or blood–brain barrier secretion (Jiang, Cowan, Moonah, & Petri, 2018). The blood–brain barrier is more permeable during childhood than in adulthood; thus, cytokines are likely to cross it in the presence of an acute childhood infection (Bilbo & Schwarz, 2012). In the central nervous system, cytokines play a normal role in autocrine and paracrine signaling; notwithstanding, recurrent infections may alter this signaling and affect neurodevelopment in several ways (Bilbo & Schwarz, 2012; Jiang, Cowan et al., 2018). First, an increase in proinflammatory cytokines due to infection can have a direct effect on neurogenesis, neuronal and glial cell migration, proliferation, and differentiation, and synaptic maturation and pruning, all vital processes in neurodevelopment. Second, cytokines can activate the hypothalamic–pituitary axis, increasing glucocorticoid production (Webster & Sternberg, 2004), and altering the metabolism of neurotransmitters including norepinephrine and serotonin (Dunn, 2006). Glucocorticoids can directly affect neurodevelopmental processes including myelination and programmed cell death (Huang, 2011), while deficits in norepinephrine (Moret & Briley, 2011) and serotonin (Van Praag, 1982) are

Author for correspondence: Eduardo Villamor, University of Michigan School of Public Health, Department of Epidemiology, 1420 Washington Heights, Ann Arbor, MI 48109, USA. E-mail: villamor@umich.edu.

Cite this article: Beer RJ, Dent KR, Robinson SL, Oliveros H, Mora-Plazas M, Marin C, Villamor E (2023). Common infectious morbidity and white blood cell count in middle childhood predict behavior problems in adolescence. *Development and Psychopathology* **35**: 301–313, https://doi.org/10.1017/S0954579421000675

commonly observed in patients with depression. Although critical neurodevelopmental events occur in utero and before 3 years of age, there is evidence that substantial synapse growth and myelination continue throughout early to middle childhood; thus, this period constitutes a key window during which infection and inflammation may impact brain development and downstream behavioral outcomes (John, Black, & Nelson, 2017).

Exposure to enteropathogens at birth has been related to decreased cognitive performance after 24 months of age (Mal-Ed Network Investigators, 2018). Further, helminthiases (Ezeamama et al., 2005), schistosomiasis (Nokes et al., 1999), and malaria (Nankabirwa et al., 2013) in middle childhood have been related to impaired cognitive development. In addition, infections requiring ambulatory or hospital treatment in infancy and childhood have been associated with subsequent development of severe mental health disorders during childhood and adolescence (Blomström et al., 2014; Köhler-Forsberg et al., 2019). The role in behavioral development of recurrent infections at life stages when they are common, including middle childhood, has not been elucidated. Evidence is also scant on the associations between biomarkers of subclinical inflammation, often resulting from recurrent infections, and neurobehavioral outcomes.

The objective of this study was to ascertain whether high incidence of common middle childhood infections was related to the development of internalizing and externalizing behavior problems in adolescence. A secondary aim was to examine the associations between biomarkers of inflammation of any grade, which may result from acute or recurrent infections, and behavior problems.

Method

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 (Arsenault et al., 2009; Robinson et al., 2018). In brief, we recruited 3,202 randomly selected children aged 5–12 years from public primary schools in February 2006. Since most children in the public school system are from low- and middle-income backgrounds, the sample pertains to these groups.

Baseline information

At the time of enrollment, 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, and household food insecurity and socioeconomic status. Household food insecurity was assessed with a validated Spanish language version of the US Department of Agriculture household food security survey module (Harrison, Stormer, Herman, & Winham, 2003) and household socioeconomic status was categorized according to the city government's classification.

During the weeks following enrollment, trained research assistants visited participating children at their schools to perform anthropometric measurements. Height was measured without shoes to the nearest 1 mm using a wall-mounted portable Seca 202 stadiometer (Seca, Hanover, MD) and weight was measured in light clothing to the nearest 0.1 kg using Tanita H5301 electronic scales (Tanita, Arlington Heights, IL). At the same visits, a fasting blood sample was obtained through antecubital venipuncture. One aliquot was collected in a tube coated with ethylenediaminetetraacetic acid, and a second one in a metal-free polypropylene tube without anticoagulant for separation of serum. The samples were protected from sunlight and transported in refrigerated coolers on the day of collection to the Colombian National Institute of Health, where they were processed and cryostored for future analyses.

Throughout the academic year following enrollment into the cohort, parents or primary caregivers kept daily records of morbidity episodes using a 7-day pictorial diary that was distributed and returned on a weekly basis. The diaries had drawings depicting children with symptoms including vomiting, diarrhea, 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, including randomized controlled trials in which illness is defined according to clinical symptoms (Blanken et al., 2013; Martin, Fairchok, Stednick, Kuypers, & Englund, 2013; Pappas, Hendley, Hayden, & Winther, 2008). The use of symptom diaries has been validated in various settings (Stanton et al., 1987; Watson, Little, Moore, Warner, & Williamson, 2001), and previous studies indicate that pictorial diaries validly capture incidence of morbidity in low- and middle-income countries (Goldman, Vaughan, & Pebley, 1998; Wright et al., 2006).

Follow-up

Between 2011 and 2015 we conducted an in-person follow-up assessment in a random sample of approximately one-third of cohort members ($n = 1{,}139$). At this assessment, we ascertained adolescent behavior from the parents' and child's perspectives with use of the Spanish language versions of the child behavior checklist (CBCL) and the youth self-report (YSR) questionnaire, respectively. The CBCL has been validated for use in children aged 5–18 years (Achenbach & Rescorla, 2001), has high reliability (Achenbach et al., 1990), and has been utilized in Brazil (Borsa, 2015) and Colombia (Hewitt-Ramírez et al., 2014). The YSR has been validated for use in adolescents aged 11–18 years (Achenbach & Rescorla, 2001) and has high reliability (Achenbach et al., 1990). It is also generalizable to Spanish-speaking populations (Ivanova et al., 2007) and has been utilized in studies of Chilean (Lozoff, Castillo, Clark, Smith, & Sturza, 2014), Costa Rican (Corapci, Calatroni, Kaciroti, Jimenez, & Lozoff, 2010), and Puerto Rican (Achenbach et al., 1990) adolescents. Both instruments consist of 112 statements about behaviors and feelings that the respondents rate as false, sometimes true, or very often true. From responses to these questions, an assessment data manager software (Achenbach System of Empirically Based Assessment, 2010) calculates continuous scores for eight behavior problem subscales: aggressive behavior, rule breaking behavior, anxious/depressed, withdrawn/depressed, somatic complaints, attention problems, social problems, and thought problems. The sum of the anxious/depressed, withdrawn/depressed, and somatic complaints subscale scores comprise the internalizing problems score and the sum of the aggressive and rule breaking behavior subscale scores constitute the externalizing problems score (Bordin et al., 2013). The assessment data manager software standardizes scores by age and sex to a reference population derived from data collected periodically in US national surveys (Achenbach System of Empirically Based Assessment, 2010).

The parents or primary caregivers of all children gave written informed consent prior to enrollment in the study and before

https://doi.org/10.1017/S0954579421000675 Published online by Cambridge University Press

Table 1. Infectious morbidity symptoms in middle childhood and total internalizing problems in adolescence among schoolchildren from Bogotá, Colombia

	Child behavior checklist (parent report) (CBCL)				Youth self-report (YSR)			
Number of days with symptoms per year[a]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[b]	Adjusted difference (95% CI)[c]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[b]	Adjusted difference (95% CI)[c]
Diarrhea with vomiting								
None	708	56.5 ± 9.9	Reference	Reference	882	53.7 ± 9.9	Reference	Reference
Moderate	60	58.9 ± 9.1	2.4 (−0.1, 4.8)	2.5 (0.1, 4.9)	69	54.4 ± 10.6	0.7 (−1.9, 3.3)	0.7 (−2.0, 3.3)
High	50	57.9 ± 7.9	1.3 (−1.0, 3.6)	0.9 (−1.4, 3.3)	65	54.2 ± 10.1	0.5 (−2.0, 3.0)	1.0 (−1.7, 3.7)
p, trend[d]			0.13	0.21			0.62	0.43
Cough with fever								
None	600	56.4 ± 9.8	Reference	Reference	743	53.6 ± 10.1	Reference	Reference
Moderate	113	56.9 ± 9.8	0.5 (−1.4, 2.5)	0.3 (−1.6, 2.3)	135	54.2 ± 8.8	0.6 (−1.0, 2.3)	0.4 (−1.3, 2.1)
High	105	59.0 ± 9.4	2.6 (0.6, 4.6)	3.1 (1.1, 5.2)	138	54.3 ± 9.9	0.6 (−1.2, 2.5)	0.7 (−1.3, 2.7)
p, trend			0.01	0.005			0.46	0.47
Earache/discharge with fever								
None	754	56.7 ± 9.7	Reference	Reference	938	53.6 ± 10.0	Reference	Reference
Moderate	33	56.7 ± 12.0	0.1 (−4.0, 4.2)	0.2 (−3.9, 4.2)	39	56.4 ± 9.6	2.8 (−0.2, 5.9)	2.8 (−0.2, 5.8)
High	31	60.2 ± 9.1	3.5 (0.3, 6.7)	2.6 (−0.9, 6.0)	39	55.3 ± 8.3	1.6 (−1.0, 4.3)	2.3 (−0.5, 5.2)
p, trend			0.06	0.19			0.10	0.04
Fever								
None	456	56.0 ± 9.8	Reference	Reference	561	53.5 ± 10.1	Reference	Reference
Low	120	57.3 ± 9.9	1.3 (−0.7, 3.3)	0.5 (−1.6, 2.5)	149	54.7 ± 9.1	1.2 (−0.5, 2.9)	0.6 (−1.2, 2.4)
Moderate	136	57.7 ± 9.5	1.7 (−0.1, 3.5)	1.6 (−0.3, 3.6)	160	53.6 ± 10.4	0.1 (−1.7, 1.9)	0.1 (−1.9, 2.0)
High	106	58.5 ± 9.6	2.5 (0.4, 4.5)	1.7 (−0.4, 3.9)	146	54.0 ± 9.5	0.5 (−1.2, 2.2)	0.4 (−1.4, 2.3)
p, trend			0.01	0.08			0.69	0.70

[a]Moderate and high number of days per year correspond to values < versus ≥ the median for children with rates >0. Medians (days per year) are 4.6, 6.6, and 3.9 for diarrhea with vomiting, cough with fever, and earache/discharge with fever, respectively. For fever, low, moderate, and high are tertiles of the distribution among children with rates >0 and correspond to cut points (days per year) 4.7 and 13.5, respectively.

[b]From linear regression models with total internalizing behavior problems score as the continuous 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 linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

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

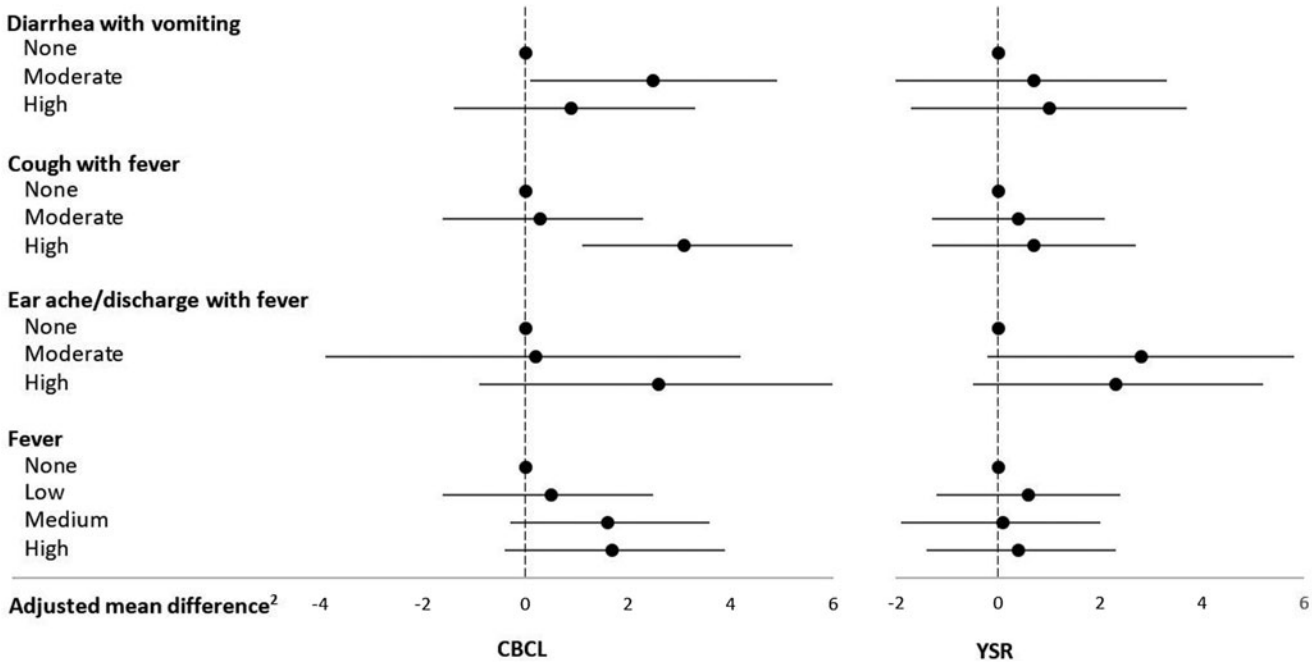

Figure 1. Infectious morbidity symptoms (days per year)[1] in middle childhood and total internalizing problems in adolescence among schoolchildren from Bogotá, Colombia. CBCL: child behavior checklist (parent report); YSR: youth self-report. [1]Moderate and high number of days per year correspond to values < versus ≥ the median for children with rates >0. Medians (days per year) are 4.6, 6.6, and 3.9 for diarrhea with vomiting, cough with fever, and earache/discharge with fever, respectively. For fever, low, moderate, and high are tertiles of the distribution among children with rates >0 and correspond to cut points (days per year) 4.7 and 13.5, respectively. [2]Horizontal lines represent 95% confidence intervals. Estimates are from linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

participation in the follow-up assessment. Youth gave written assent to participate. 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.

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 analyzer (Bayer Diagnostics, Tarrytown, NY). Plasma ferritin and vitamin B_{12} were quantified using a competitive chemiluminescent immunoassay in an ADVIA Centaur analyzer (Bayer Diagnostics, Tarrytown, NY).

Data analysis

Outcomes

Primary outcomes were total internalizing and externalizing behavior problem scores per the CBCL and YSR. Secondary outcomes were the individual subscale scores.

Exposures

The exposures of interest were (a) infectious morbidity in middle childhood, (b) white blood cell (WBC) counts at baseline, and (c) serum CRP concentrations at baseline. Infectious morbidity exposures were defined using the parental report of symptoms on the pictorial diaries administered during the first year of follow-up. We defined three syndromes to represent infectious morbidity by combining symptoms reported on the same day in the pictorial diaries: diarrhea with vomiting, cough with fever, and earache or ear discharge with fever. Diarrhea with vomiting has been related to clinically diagnosed episodes of gastrointestinal illness (Arias et al., 2010; Rockx et al., 2002; Staat et al., 2002). Cough with fever had a positive predictive value of 83% for laboratory-confirmed influenza infection among children 5–12 years old (Ohmit & Monto, 2006), and this case definition has been used to monitor influenza-like illness in Latin America (Gordon et al., 2009). Cough with fever is also reported in school-age children experiencing the common cold due to a variety of viral and bacterial infections (Pappas et al., 2008). Although the diagnosis of acute otitis media requires clinical examination, symptoms including moderate to severe ear pain with fever are indicators of severe illness (Lieberthal et al., 2013) and ear drainage is often related to bacterial infection (Chen, Hsieh, Huang, & Chiu, 2013). We also considered any fever (alone or in combination with any other symptom) as an unspecific infection surrogate. Because there is not a conventionally accepted categorization of morbidity rates in middle childhood, we used the study population distributions to define morbidity levels as previously done in other populations (Grüber et al., 2008; Ramette et al., 2018). Since a majority of children had no episodes, zero rates ("none") were the reference category for all infectious syndromes. Next, among children with at least one episode, we used quantiles of the distributions. For fever, we divided children with rates >0 into three equal-sized groups (tertiles) (Grüber et al., 2008), representing "low," "moderate," or "high" rates, respectively. For all other syndromes, reduced variability in rates >0 prevented us from using tertiles; thus, we divided the population with non-zero rates as under versus at or above

https://doi.org/10.1017/S0954579421000675 Published online by Cambridge University Press

Table 2. Infectious morbidity symptoms in middle childhood and total externalizing problems in adolescence among schoolchildren from Bogotá, Colombia

	Child behavior checklist (parent report) (CBCL)				Youth self-report (YSR)			
Number of days with symptoms per year[a]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[b]	Adjusted difference (95% CI)[c]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[b]	Adjusted difference (95% CI)[c]
Diarrhea with vomiting								
None	708	55.5 ± 9.2	Reference	Reference	882	52.6 ± 9.6	Reference	Reference
Moderate	60	56.1 ± 9.4	0.5 (−2.0, 3.0)	1.0 (−1.4, 3.5)	69	52.8 ± 10.5	0.1 (−2.5, 2.7)	0.7 (−1.9, 3.4)
High	50	56.5 ± 8.5	0.9 (−1.5, 3.4)	0.5 (−2.2, 3.2)	65	51.6 ± 8.6	−1.1 (−3.3, 1.1)	−1.1 (−3.6, 1.4)
p, trend[d]			0.42	0.60			0.38	0.48
Cough with fever								
None	600	55.6 ± 9.2	Reference	Reference	743	52.8 ± 9.5	Reference	Reference
Moderate	113	55.4 ± 8.2	−0.1 (−1.8, 1.6)	−0.1 (−1.8, 1.6)	135	52.1 ± 9.6	−0.7 (−2.4, 1.0)	−1.0 (−2.7, 0.8)
High	105	56.3 ± 10.0	0.7 (−1.3, 2.8)	1.3 (−0.9, 3.5)	138	51.6 ± 10.1	−1.2 (−3.0, 0.6)	−0.1 (−2.1, 1.8)
p, trend			0.49	0.27			0.18	0.81
Earache/discharge with fever								
None	754	55.5 ± 9.2	Reference	Reference	938	52.4 ± 9.7	Reference	Reference
Moderate	33	55.4 ± 7.9	−0.2 (−2.9, 2.6)	0.0 (−2.7, 2.7)	39	55.3 ± 8.3	2.9 (0.3, 5.5)	3.0 (0.6, 5.3)
High	31	58.5 ± 9.7	3.0 (−0.4, 6.4)	1.5 (−2.5, 5.5)	39	53.7 ± 8.0	1.3 (−1.3, 3.8)	1.5 (−1.5, 4.6)
p, trend			0.12	0.49			0.14	0.12
Fever								
None	456	55.4 ± 9.2	Reference	Reference	561	52.7 ± 9.6	Reference	Reference
Low	120	56.1 ± 8.9	0.7 (−1.0, 2.5)	0.2 (−1.7, 2.1)	149	52.5 ± 9.5	−0.2 (−1.9, 1.5)	−0.9 (−2.7, 0.9)
Moderate	136	55.5 ± 9.3	0.1 (−1.7, 1.8)	0.3 (−1.6, 2.1)	160	53.2 ± 9.9	0.5 (−1.2, 2.3)	0.9 (−0.9, 2.7)
High	106	56.3 ± 9.3	1.0 (−1.0, 2.9)	0.4 (−1.7, 2.5)	146	51.3 ± 9.5	−1.4 (−3.1, 0.3)	−0.8 (−2.6, 1.1)
p, trend			0.39	0.71			0.15	0.62

[a]Moderate and high number of days per year correspond to values < versus ≥ the median for children with rates >0. Medians (days per year) are 4.6, 6.6, and 3.9 for diarrhea with vomiting, cough with fever, and earache/discharge with fever, respectively. For fever, low, moderate, and high are tertiles of the distribution among children with rates >0 and correspond to cut points (days per year) 4.7 and 13.5, respectively.

[b]From linear regression models with total externalizing behavior problems score as the continuous 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 linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

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

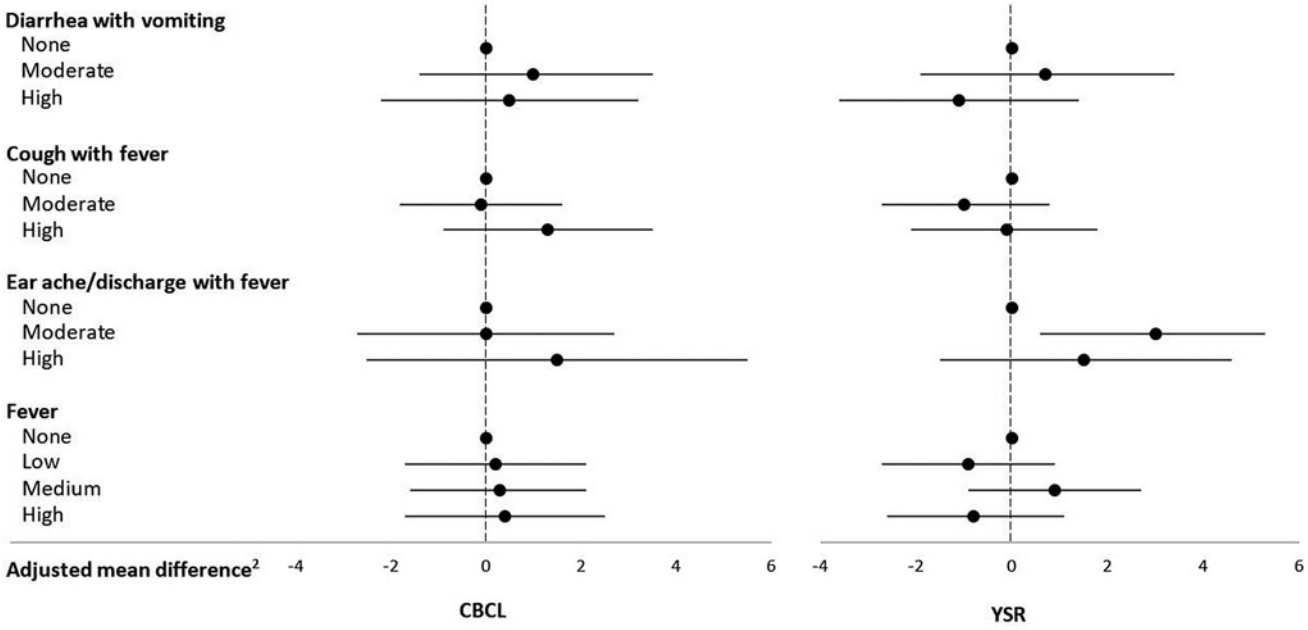

Figure 2. Infectious morbidity symptoms (days per year)[1] in middle childhood and total externalizing problems in adolescence among schoolchildren from Bogotá, Colombia. CBCL: child behavior checklist (parent report); YSR: youth self-report. [1]Moderate and high number of days per year correspond to values < versus ≥ the median for children with rates >0. Medians (days per year) are 4.6, 6.6, and 3.9 for diarrhea with vomiting, cough with fever, and earache/discharge with fever, respectively. For fever, low, moderate, and high are tertiles of the distribution among children with rates >0 and correspond to cut points (days per year) 4.7 and 13.5, respectively. [2]Horizontal lines represent 95% confidence intervals. Estimates are from linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

the median rate, to represent "moderate" or "high" rates, respectively. Rates were not considered as continuous variables in the analyses because they were highly overdispersed. WBC is an established biomarker for infection and inflammation in clinical practice; it has been used in pediatric population studies to assess chronic inflammation (Abramson & Melton, 2000; Adelantado-Renau, Beltran-Valls, Mota, & Moliner-Urdiales, 2020). High WBC has been related to cardiometabolic risk factors in this (Gilbert-Diamond, Baylin, Mora-Plazas, & Villamor, 2012) and other (Lee et al., 2010; Park, Lee, & Lee, 2017) pediatric surveys, supporting the notion that increased WBC may serve as a low-cost marker of inflammation, which may result from frequent infections. Elevated WBC count was defined as >10,000/mm^3. Among children, the normal WBC range is between 5,000 and 10,000. Values above 10,000 are clinically significant (Cleveland Clinic, 2018). WBC was also considered as a continuous predictor. CRP is a low-cost, validated, frequently used biomarker to detect systemic inflammation (Abramson & Melton, 2000; Singh & Newman, 2011; Stolzman & Bement, 2012). Elevated CRP was defined as >3.0 mg/L, which has been previously used to define low-grade systemic inflammation in children (Broyles et al., 2012; Lande et al., 2008). CRP was also considered as a continuous predictor after logarithmic transformation.

Statistical analysis

Of the 1,139 children in the follow-up assessment, 1,044 (92%) had valid information on the CBCL or the YSR. Twenty-six children with missing morbidity data in middle childhood were excluded, resulting in a final analytic sample of 1,018 children (818 with CBCL and 1,016 with YSR). Compared with cohort participants excluded from analyses, children in the analytic sample had higher rates of diarrhea with vomiting, cough with fever, and any fever, but these differences were not statistically significant (see Table 1 in the Supplementary Material). They were also more likely to be female, were slightly younger, and had better educated mothers.

We compared the continuous distribution of internalizing and externalizing behavior problem scores between categories of each exposure using means and standard deviation, *SD*. Next, we estimated adjusted mean differences and 95% confidence intervals (CI) with use of linear regression models. Confounders were independent predictors of behavior problems as previously reported in this population (Robinson et al., 2018). These included child's sex, age, baseline iron deficiency (serum ferritin <15 μg/l in children with CRP ≤10 mg/l), hemoglobin, and low plasma vitamin B_{12} concentrations, mother's education, household food insecurity with hunger, and low socioeconomic status. Children with CRP >10 mg/l were excluded from multivariable models because iron deficiency per serum ferritin, an adjustment covariate, is undefined in this group. Tests for linear trend were carried out by introducing into the models a variable representing ordinal categories of the exposure as a continuous covariate. Because there were 50 sibling pairs and 1 triplet, all models specified robust variances and accounted for correlations between siblings. Analyses were performed with use of the Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC).

Results

Mean ± *SD* children's age at baseline was 8.5 ± 1.6 years and 14.7 ± 1.7 years at follow-up; 56.2% were girls (see Table 1 in the Supplementary Material). Median follow-up was 6.1 years (mean ± *SD*: 6.2 ± 1.0 years, range: 5.2–9.5 years). Children

https://doi.org/10.1017/S0954579421000675 Published online by Cambridge University Press

Table 3. Inflammatory biomarkers in middle childhood and total internalizing problems in adolescence among schoolchildren from Bogotá, Colombia

	Child behavior checklist (parent report) (CBCL)				Youth self-report (YSR)			
Inflammatory biomarker	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]
White blood cell count								
≤10,000 /mm^3	667	56.6 ± 9.7	Reference	Reference	830	53.7 ± 9.8	Reference	Reference
>10,000 /mm^3	49	59.5 ± 8.6	2.9 (0.4, 5.4)	2.9 (0.3, 5.5)	61	55.9 ± 9.7	2.1 (−0.4, 4.6)	2.9 (0.1, 5.6)
p[c]			0.03	0.04			0.10	0.05
Per 1,000/mm^3	716		0.0 (−0.3, 0.3)	0.0 (−0.3, 0.4)	891		0.1 (−0.2, 0.4)	0.3 (−0.1, 0.6)
p			0.93	0.79			0.40	0.09
C-reactive protein								
≤3 mg/l	682	56.9 ± 9.8	Reference	Reference	844	54.1 ± 9.9	Reference	Reference
>3 mg/	59	56.4 ± 9.4	−0.5 (−3.0, 2.0)	−0.3 (−2.8, 2.2)	78	52.6 ± 10.6	−1.5 (−3.9, 1.0)	−1.2 (−3.9, 1.5)
p			0.71	0.82			0.24	0.39
Per 100% difference	741		0.1 (−0.4, 0.5)	0.1 (−0.4, 0.6)	922		−0.2 (−0.6, 0.2)	−0.3 (−0.7, 0.1)
p			0.80	0.68			0.26	0.17

[a]From linear regression models with total internalizing behavior problems score as the continuous outcome and indicator variables for each inflammatory biomarker as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.
[b]From linear regression models adjusted for child's sex, age, and iron deficiency at baseline, household food insecurity with hunger, and mother's education. Robust estimates of variance were used in all models to account for correlations between siblings.
[c]Wald test.

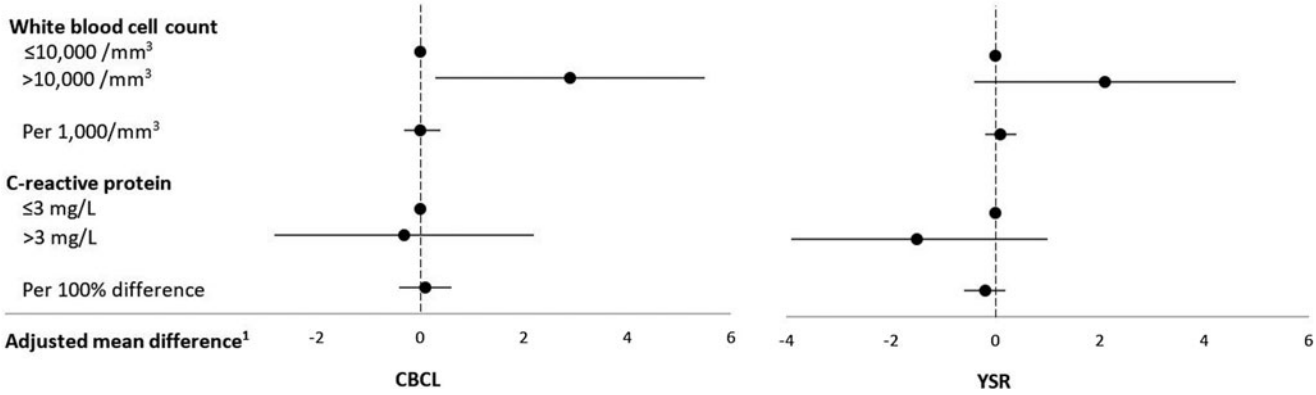

Figure 3. Inflammatory biomarkers in middle childhood and total internalizing problems in adolescence among schoolchildren from Bogotá, Colombia. CBCL: child behavior checklist (parent report); YSR: youth self-report. [1]Horizontal lines represent 95% confidence intervals. Estimates are from linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

contributed 126,877 days of observation for infectious morbidity during the first follow-up year (median per child, 133; interquartile range, 77, 175). Annual morbidity rates (days per child-year) of diarrhea with vomiting, cough with fever, ear pain/ear discharge with fever, and fever were, respectively, 1.0, 3.2, 0.7, and 5.9. Mean ± *SD* baseline WBC was 7,137 ± 2,071/mm^3 and 6.9% had WBC >10,000/mm^3. Mean ± *SD* CRP was 1.4 ± 2.5 mg/l, 7.7% had CRP >3.0 mg/l and 1.3% had values >10.0 mg/l, a cut point suggestive of an acute infection.

Morbidity in middle childhood and internalizing problems in adolescence

Mean ± *SD* CBCL and YSR internalizing problems scores were, respectively, 56.8 ± 9.8 and 53.8 ± 9.9. Diarrhea with vomiting and cough with fever rates were positively related to the CBCL internalizing problems score (Table 1, Figure 1). The mean score of children who experienced moderate diarrhea with vomiting (>0 to ≤4.6 days/year) was an adjusted 2.5 (95% CI: 0.1, 4.9; $p = .04$) units higher than that of children without these symptoms. High cough with fever rates (≥6.6 days/year) were related to an adjusted 3.1 (95% CI: 1.1, 5.2; $p = .003$) units higher mean CBCL internalizing problems score compared with zero rates. High cough with fever rates were also related to increased CBCL somatic complaints (see Table 2 in the Supplementary Material) and anxious/depressed (see Table 3 in the Supplementary Material) subscale scores. Earache/discharge with fever was positively associated with higher CBCL somatic complaints subscale scores (see Table 2 in the Supplementary Material), whereas high fever rates (≥13.5 days/year) were related to increased CBCL anxious/depressed subscale scores (see Table 3 in the Supplementary Material). There were no associations with the withdrawn/depressed subscale (see Table 4 in the Supplementary Material).

Morbidity in middle childhood and externalizing problems in adolescence

Mean ± *SD* CBCL and YSR externalizing problems scores were, respectively, 55.6 ± 9.2 and 52.6 ± 9.6. Earache/discharge with fever was associated with increased YSR externalizing behavior problems score (Table 2, Figure 2). Other morbidity rates were not associated with externalizing problems per the CBCL or the YSR overall or with the rule-breaking (see Table 5 in the Supplementary Material) or aggressive behavior (see Table 6 in the Supplementary Material) subscales.

Inflammatory biomarkers in middle childhood and internalizing problems in adolescence

WBC count was positively associated with internalizing problem scores (Table 3, Figure 3). Compared with children whose WBC counts were ≤10,000/mm^3, those with WBC >10,000/mm^3 had an adjusted 2.9 (95% CI: 0.3, 5.5, $p = .04$) and 2.9 (95% CI: 0.1, 5.6, $p = .05$) units higher CBCL and YSR internalizing behavior score, respectively. Although WBC count was not associated with the somatic complaints (see Table 7 in the Supplementary Material) or the anxious/depressed (see Table 8 in the Supplementary Material) subscale scores, WBC counts >10,000/mm^3 were positively related to YSR withdrawn/depressed scores (see Table 9 in the Supplementary Material). CRP plasma concentrations were not associated with internalizing problems scores (Table 3) or its subscales (see Tables 7–9 in the Supplementary Material).

Inflammatory biomarkers in middle childhood and externalizing problems in adolescence

Neither WBC counts nor CRP plasma concentrations were associated with total externalizing problems in adolescence (Table 4, Figure 4) or its subscales (see Tables 10 and 11 in the Supplementary Material).

Discussion

In this longitudinal investigation of low- and middle-income Colombian school children, gastrointestinal and respiratory infectious morbidity in middle childhood was associated with internalizing behavior problems in adolescence. The association with respiratory morbidity, including cough with fever and otitis media, was driven by associations with the somatic complaints subscale, whereas fever of any origin was related to increased anxious/depressed scores. Elevated WBC count, a marker of

https://doi.org/10.1017/S0954579421000675 Published online by Cambridge University Press

Table 4. Inflammatory biomarkers in middle childhood and total externalizing problems in adolescence among schoolchildren from Bogotá, Colombia

	Child behavior checklist (parent report) (CBCL)				Youth self-report (YSR)			
Inflammatory biomarker	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]	*n*	Mean ± *SD*	Unadjusted difference (95% CI)[a]	Adjusted difference (95% CI)[b]
White blood cell count								
≤10,000 /mm^3	667	55.6 ± 9.1	Reference	Reference	830	52.6 ± 9.7	Reference	Reference
>10,000 /mm^3	49	56.0 ± 8.9	0.4 (−2.2, 2.9)	0.2 (−2.4, 2.9)	61	53.4 ± 9.8	0.8 (−1.7, 3.3)	2.2 (−0.5, 4.9)
p[c]			0.76	0.86			0.54	0.12
Per 1,000/mm^3	716		−0.1 (−0.4, 0.2)	−0.1 (−0.5, 0.2)	891		−0.1 (−0.4, 0.2)	0.1 (−0.2, 0.4)
P			0.60	0.44			0.47	0.63
C-reactive protein								
≤3 mg/l	682	55.7 ± 9.2	Reference	Reference	844	52.8 ± 9.6	Reference	Reference
>3 mg/l	59	55.1 ± 9.7	−0.6 (−3.2, 1.9)	−1.4 (−4.1, 1.2)	78	51.7 ± 10.6	−1.1 (−3.5, 1.4)	−1.6 (−4.1, 0.9)
p			0.63	0.29			0.39	0.22
Per 100% difference	741		0.2 (−0.2, 0.6)	0.1 (−0.4, 0.5)	922		0.1 (−0.3, 0.4)	−0.1 (−0.5, 0.3)
p			0.35	0.69			0.79	0.50

[a]From linear regression models with total externalizing behavior problems score as the continuous outcome and indicator variables for each inflammatory biomarker as predictors. Robust estimates of variance were used in all models to account for correlations between siblings.
[b]From linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, low socioeconomic status, household food insecurity with hunger, and mother's education. Robust estimates of variance were used in all models to account for correlations between siblings.
[c]Wald test.

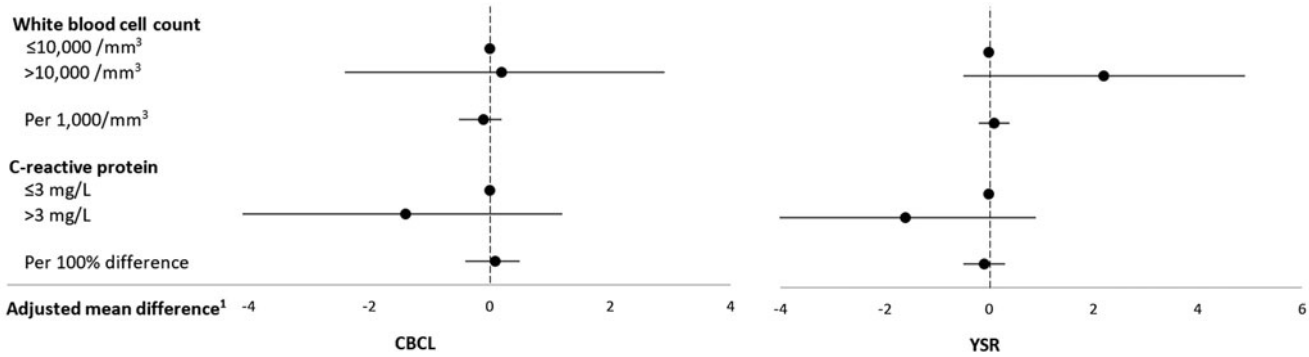

Figure 4. Inflammatory biomarkers in middle childhood and total externalizing problems in adolescence among schoolchildren from Bogotá, Colombia. CBCL: child behavior checklist (parent report); YSR: youth self-report. [1]Horizontal lines represent 95% confidence intervals. Estimates are from linear regression models adjusted for child's sex, age, iron deficiency, anemia, and low vitamin B_{12} at baseline, mother's education, household food insecurity with hunger, and low socioeconomic status. Robust estimates of variance were used in all models to account for correlations between siblings.

inflammation, was also associated with internalizing behavior problems, through the withdrawn/depressed subscale.

Previous studies reported associations between infectious morbidity in childhood and neurocognitive and behavioral development or psychiatric illness later in life. A population-based cohort study in Denmark found that postnatal infections requiring outpatient or hospital treatment were associated with subsequent risk of severe mental disorders (Köhler-Forsberg et al., 2019), whereas childhood infection-related hospital admission in Sweden was related to risk of nonaffective psychoses in adolescence (Blomström et al., 2014). Inflammatory biomarkers have also been related to mental health outcomes in previous studies. For instance, in the Avon longitudinal study of parents and children, interleukin (IL)-6 at age 9 years was associated with depression and psychosis at age 18 years (Khandaker, Pearson, Zammit, Lewis, & Jones, 2014) and hypomanic symptoms at age 22 years (Hayes et al., 2017) in a dose–response manner. CRP and IL-6 in adulthood also predicted risk of depression in Denmark (Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013) and Britain (Gimeno et al., 2009). Our study extends previous findings by focusing on common middle childhood infections, including respiratory and gastrointestinal illness, which may not be severe enough to warrant treatment. The association of high WBC with internalizing behavior problems is a novel finding. Because WBC is often elevated in the presence of infection, the results are internally consistent.

There are different possible explanations for an association between pediatric infectious morbidity and neurobehavioral development. First, high infection rates during middle childhood resulting from increased exposure or susceptibility to infectious agents could lead to a sustained subclinical inflammatory response. Chronic inflammation could alter brain development through several pathways. Pro-inflammatory signals produced by the immune system can disrupt and increase the permeability of the blood–brain barrier and induce crossing of cells and cytokines that may directly interact with neuronal projections, potentially affecting brain function (Banks & Erickson, 2010). Pro-inflammatory cytokines might also induce microglia activation, which affects brain development through impaired neurogenesis and dendritic arborization, neurotransmitter dysregulation, and glial proliferation (Hagberg & Carina, 2005). Furthermore, pro-inflammatory cytokines may alter the expression of glutamate receptors through the kynurenine pathway (John et al., 2017), and activate the hypothalamus–pituitary–adrenal axis, resulting in increased cortisol production and glucocorticoid resistance (Ratnayake, Quinn, Walker, & Dickinson, 2013). Nitric oxide, which is produced by macrophages in response to infectious pathogens, might affect neuronal proliferation, differentiation, and synaptogenesis (Banks & Erickson, 2010; Gibbs, 2003; Tripathi, 2007). These pathways have been involved in the development of mood, anxiety, and psychotic disorders (Nawa & Takei, 2006; Pariante & Lightman, 2008; Tsapakis & Travis, 2002). Second, we noted that the associations between infectious morbidity and internalizing behavior problems were more consistent for the parental report than the self-report, and some of these associations were largely explained through the somatic complaints subscale. It is plausible that parents of children with a high infection burden perceive them as more vulnerable than they may be and induce internalization behaviors (De Ocampo, Macias, Saylor, & Katikaneni, 2003). Third, the somatic complaints subscale in the CBCL comprises questions on physical symptoms including constipation, dizziness, tiredness, aches, nausea, cramps, and vomiting (Read et al., 2015). If the morbidity burden observed during 1 year in middle childhood tracked into adolescence, increased somatic complaints scores could simply reflect an expression of symptoms from frequent illness. Nonetheless, previous research suggests that high parent-reported somatic complaints scores are indicative of somaticizing behavior rather than pain experiences from illness (Campo & Fritsch, 1994; Eisman, Fogel, Lazarovich, & Pustilnik, 2007); thus, somatic complaints may have a psychological rather than a physical basis.

This study has several strengths. The longitudinal design minimizes the possibility of reverse causation bias. Prospective collection of exposure and outcome information precludes misclassification due to recall bias. The use of two complementary scales enhances the validity of outcome assessment since some behaviors may be more or less likely to be reported by adolescents compared to their parents. Finally, the consistency of associations with self-reported morbidity and objectively determined WBC increases the internal validity of the study.

Some limitations are also worth noting. First, reverse causation cannot be completely ruled out if behavior problems were already present in middle childhood; we did not have an opportunity to ascertain them at baseline. Nonetheless, many of these problems only become manifest during adolescence. Second, the analytic sample differed from the group of children excluded from the analyses with respect to the distribution of exposure and some predictors of outcome status; this could lead to selection bias. Third, a single measure of WBC or CRP may not represent

https://doi.org/10.1017/S0954579421000675 Published online by Cambridge University Press

chronic subclinical inflammation since their values can increase acutely in response to an infectious episode and may be subject to large within-person variation. Fourth, we lacked information on the etiologic agents of infectious morbidity; this could have provided mechanistic clues. We also lacked information on whether the episodes required treatment. Fifth, residual confounding by unmeasured variables including adverse childhood experiences cannot be discarded. Adverse childhood experiences including foster care and adoption have been related both to gastrointestinal symptoms and anxiety in children and adolescents (Callaghan et al., 2020). Sixth, because there are no agreed-upon categorizations of infectious morbidity in middle childhood, we used distribution-driven definitions of rate cut points and levels and this may limit the comparability of results with other populations. Nevertheless, some of the cut points for high rates that resulted from categorizing them into quantiles seem consistent with those reported in other studies. For example, German schoolchildren had a mean 1.3 common cold episodes per year, each lasting about one week (Grüber et al., 2008); the definition of high rates of cough with fever in our study (≥7 days/year) would approximately correspond to being above the mean in the German study. Finally, Type I error may be enhanced by analyzing a large number of outcomes; thus, we cannot rule out chance as an explanation for the associations observed.

In conclusion, gastrointestinal and respiratory morbidity and high WBC in middle childhood are associated with internalizing behavior problems in adolescence. Whether decreasing the burden of common infections results in improved neurobehavioral outcomes warrants further investigation.

Supplementary Material. The supplementary material for this article can be found at https://doi.org/10.1017/S0954579421000675

Author Contributions. Rachael J. Beer and Kallisse R. Dent contributed equally to this work.

Funding Statement. This work was supported by the ASISA Research Fund at the University of Michigan.

Conflicts of Interest. None.

References

Abramson, N., & Melton, B. (2000). Leukocytosis: Basics of clinical assessment. *American Family Physician*, *62*, 2053–2060.

Achenbach, T. M., Bird, H. R., Canino, G., Phares, V., Gould, M. S., & Rubio-Stipec, M. (1990). Epidemiological comparisons of Puerto Rican and U.S. mainland children: Parent, teacher, and self-reports. *Journal of the American Academy of Child & Adolescent Psychiatry*, *29*, 84–93. doi:10.1097/00004583-199001000-00014

Achenbach, T. M., & Rescorla, L. A. (2001). *Manual for the ASEBA school-age forms & profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach System of Empirically Based Assessment. (2010). *User guide for assessment data manager (ADM): CBCL, YSR, TFR, ASR, ABCL, OASR, OABCL, YASR, YABCL, SCICA, CBCL/2–3, CBCL/1.5-5, C-TRF, T0F & DOF*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Adelantado-Renau, M., Beltran-Valls, M. R., Mota, J., & Moliner-Urdiales, D. (2020). Circulating inflammatory biomarkers and academic performance in adolescents: DADOS study. *PLoS One*, *15*(11), e0242016. doi:10.1371/journal.pone.0242016

Arias, C., Sala, M., Dominguez, A., Torner, N., Ruiz, L., Martinez, A., … Buesa, J. (2010). Epidemiological and clinical features of norovirus gastroenteritis in outbreaks: A population-based study. *Clinical Microbiology and Infection*, *16*, 39–44. doi:10.1111/j.1469-0691.2009.02831.x

Arsenault, J. E., Mora-Plazas, M., Forero, Y., Lopez-Arana, S., Marin, C., Baylin, A., & Villamor, E. (2009). Provision of a school snack is associated with vitamin B-12 status, linear growth, and morbidity in children from Bogota, Colombia. *Journal of Nutrition*, *139*, 1744–1750. doi:10.3945/jn.109.108662

Banks, W. A., & Erickson, M. A. (2010). The blood-brain barrier and immune function and dysfunction. *Neurobiology of Disease*, *37*, 26–32. doi:10.1016/j.nbd.2009.07.031

Bilbo, S. D., & Schwarz, J. M. (2012). The immune system and developmental programming of brain and behavior. *Frontiers in Neuroendocrinology*, *33*(3), 267–286. doi:10.1016/j.yfrne.2012.08.006

Blanken, M. O., Rovers, M. M., Molenaar, J. M., Winkler-Seinstra, P. L., Meijer, A., Kimpen, J. L., & Bont, L. (2013). Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. *New England Journal of Medicine*, *368*, 1791–1799. doi:10.1056/NEJMoa1211917

Blomström, Å, Karlsson, H., Svensson, A., Frisell, T., Lee, B., Dal, H., … Dalman, C. (2014). Hospital admission with infection during childhood and risk for psychotic illness – a population-based cohort study. *Schizophrenia Bulletin*, *40*, 1518–1525. doi:10.1093/schbul/sbt195

Bordin, I. A., Rocha, M. M., Paula, C. S., Teixeira, M. C., Achenbach, T. M., Rescorla, L. A., & Silvares, E. F. (2013). Child behavior checklist (CBCL), youth self-report (YSR) and teacher's report form (TRF): An overview of the development of the original and Brazilian versions. *Cadernos de Saude Publica*, *29*, 13–28. doi:10.1590/s0102-311×2013000100004

Borsa, J. (2015). Reliability of the child behavior checklist and teacher's report form in a sample of Brazilian children. *Universitas Psychologica*, *14*, 15–22.

Broyles, S. T., Staiano, A. E., Drazba, K. T., Gupta, A. K., Sothern, M., & Katzmarzyk, P. T. (2012). Elevated C-reactive protein in children from risky neighborhoods: Evidence for a stress pathway linking neighborhoods and inflammation in children. *PLoS One*, *7*(9), e45419. doi:10.1371/journal.pone.0045419

Callaghan, B. L., Fields, A., Gee, D. G., Gabard-Durnam, L., Caldera, C., Humphreys, K. L., … Tottenham, N. (2020). Mind and gut: Associations between mood and gastrointestinal distress in children exposed to adversity. *Development and Psychopathology*, *32*, 309–328. doi:10.1017/S0954579419000087

Campo, J. V., & Fritsch, S. L. (1994). Somatization in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *33*, 1223–1235. doi:10.1097/00004583-199411000-00003

Chen, Y., Hsieh, Y., Huang, Y., & Chiu, C. (2013). Clinical manifestations and microbiology of acute otitis media with spontaneous otorrhea in children. *Journal of Microbiology Immunology and Infection*, *46*, 382–388. doi:10.1016/j.jmii.2013.04.001

Cleveland Clinic. (2018). High White Blood Cell Count. Retrieved from https://my.clevelandclinic.org/health/diagnostics/17704-high-white-blood-cell-count.

Corapci, F., Calatroni, A., Kaciroti, N., Jimenez, E., & Lozoff, B. (2010). Longitudinal evaluation of externalizing and internalizing behavior problems following iron deficiency in infancy. *Journal of Pediatric Psychology.*, *35*, 296–305. doi:10.1093/jpepsy/jsp065

De Ocampo, A., Macias, M., Saylor, C., & Katikaneni, L. (2003). Caretaker perception of child vulnerability predicts behavior problems in NICU graduates. *Child Psychiatry and Human Development*, *34*, 83–96. doi:10.1023/a:1027384306827

Dunn, A. J. (2006). Effects of cytokines and infections on brain neurochemistry. *Clinical Neuroscience Research*, *6*(1-2), 52–68. doi:10.1016/j.cnr.2006.04.002

Eisman, H. D., Fogel, J., Lazarovich, R., & Pustilnik, I. (2007). Empirical testing of an algorithm for defining somatization in children. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *16*, 124–131. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18421368

Ezeamama, A. E., Friedman, J. F., Acosta, L. P., Bellinger, D. C., Langdon, G. C., Manalo, D. L., … McGarvey, S. T. (2005). Helminth infection and cognitive impairment among Filipino children. The American Journal of Tropical Medicine and Hygiene, *72*, 540–548. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15891127

Gibbs, S. M. (2003). Regulation of neuronal proliferation and differentiation by nitric oxide. Molecular Neurobiology, *27*, 107–120. doi:10.1385/MN:27:2:107

Gilbert-Diamond, D., Baylin, A., Mora-Plazas, M., & Villamor, E. (2012). Chronic inflammation is associated with overweight in Colombian school

children. *Nutrition, Metabolism & Cardiovascular Diseases*, *22*(3), 244–251. doi:10.1016/j.numecd.2010.06.001

Gimeno, D., Kivimäki, M., Brunner, E., Elovainio, M., De Vogli, R., Steptoe, A., … Ferrie, J. (2009). Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychological *M*edicine, *39*, 413–423. doi:10.1017/S0033291708003723

Goldman, N., Vaughan, B., & Pebley, A. (1998). The use of calendars to measure child illness in health interview surveys. *International Journal of Epidemiology, 27*, 505–512. doi:10.1093/ije/27.3.505

Gordon, A., Ortega, O., Kuan, G., Reingold, A., Saborio, S., Balmaseda, A., & Harris, E. (2009). Prevalence and seasonality of influenza-like illness in children, Nicaragua, 2005–2007. Emerging *I*nfectious *D*iseases, *15*, 408–414. doi:10.3201/eid1503.080238

Grüber, C., Keil, T., Kulig, M., Roll, S., Wahn, U., Wahn, V., & Study Group, M. A. S. (2008). History of respiratory infections in the first 12 yr among children from a birth cohort. *Pediatric Allergy and Immunology*, *19*, 505–512. doi:10.1111/j.1399-3038.2007.00688.x

Hagberg, H., & Carina, M. (2005). Effect of inflammation on central nervous system development and vulnerability: Review. *Current Opinion in Neurology*, *18*, 117–123. doi:10.1097/01.wco.0000162851.44897.8f

Harrison, G., Stormer, A., Herman, D., & Winham, D. (2003). Development of a Spanish-language version of the U.S. household food security survey module. *Journal of Nutrition*, *133*, 1192–1197. doi:10.1093/jn/133.4.1192

Hayes, J., Khandaker, G., Anderson, J., Mackay, D., Zammit, S., Lewis, G., … Osborn, D. (2017). Childhood interleukin-6, C-reactive protein and atopic disorders as risk factors for hypomanic symptoms in young adulthood: A longitudinal birth cohort study. *Psychological Medicine*, *47*, 23–33. doi:10.1017/S0033291716003408

Hewitt-Ramírez, N., Gantiva, C. A., Vera Maldonado, A., Cuervo Rodríguez, M. P., Hernández Olaya, N. L., Juárez, F., & Parada, A. J. (2014). Afectaciones psicológicas de niños y adolescentes expuestos al conflicto armado en una zona rural de Colombia. *Acta Colombiana de Psicología*, *17*, 79–89. doi:10.14718/ACP.2014.17.1.9

Huang, L. T. (2011). The link between perinatal glucocorticoids exposure and psychiatric disorders. *Pediatric Research*, *69*(5 Pt 2), 19R–25R. doi:10.1203/PDR.0b013e318212c29b

Ivanova, M. Y., Achenbach, T. M., Rescorla, L. A., Dumenci, L., Almqvist, F., Bilenberg, N., … Verhulst, F. C. (2007). The generalizability of the youth self-report syndrome structure in 23 societies. *Journal of Consulting and Clinical Psychology*, *75*, 729–738. doi:10.1037/0022-006X.75.5.729

Jiang, N. M., Cowan, M., Moonah, S. N., & Petri, W. A., Jr. (2018). The impact of systemic inflammation on neurodevelopment. *Trends in Molecular Medicine*, *24*(9), 794–804. doi:10.1016/j.molmed.2018.06.008

John, C. C., Black, M. M., & Nelson, C. A. 3rd. (2017). Neurodevelopment: The impact of nutrition and inflammation during early to middle childhood in low-resource settings. *Pediatrics*, *139*, S59–S71. doi:10.1542/peds.2016-2828H

Khandaker, G., Pearson, R., Zammit, S., Lewis, G., & Jones, P. (2014). Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: A population-based longitudinal study. *JAMA Psychiatry*, *71*, 1121–1128. doi:10.1001/jamapsychiatry.2014.1332

Köhler-Forsberg, O., Petersen, L., Gasse, C., Mortensen, P., Dalsgaard, S., Yolken, R., … Benros, M. (2019). A nationwide study in Denmark of the association between treated infections and the subsequent risk of treated mental disorders in children and adolescents. *JAMA Psychiatry*, *76*, 271–279. doi:10.1001/jamapsychiatry.2018.3428

Lande, M. B., Pearson, T. A., Vermilion, R. P., Auinger, P., & Fernandez, I. D. (2008). Elevated blood pressure, race/ethnicity, and C-reactive protein levels in children and adolescents. *Pediatrics*, *122*(6), 1252–1257. doi:10.1542/peds.2007-3162

Lee, Y., Shin, Y., Kim, J., Shim, J., Kang, D., & Lee, H. (2010). Metabolic syndrome and its association with white blood cell count in children and adolescents in Korea: the 2005 Korean National Health and Nutrition Examination Survey. *Nutrition, Metabolism & Cardiovascular Diseases*, *20*(3), 165–172. doi:10.1016/j.numecd.2009.03.017

Lieberthal, A., Carroll, A., Chonmaitree, T., Ganiats, T., Hoberman, A., Jackson, M., … Tunkel, D. E. (2013). The diagnosis and management of acute otitis media. *Pediatrics*, *131*, e964–e999. doi:10.1542/peds.2012-3488

Lozoff, B., Castillo, M., Clark, K., Smith, J., & Sturza, J. (2014). Iron supplementation in infancy contributes to more adaptive behavior at 10 years of age. *Journal of Nutrition*, *144*, 838–845. doi:10.3945/jn.113.182048

Mal-Ed Network Investigators. (2018). Early childhood cognitive development is affected by interactions among illness, diet, enteropathogens and the home environment: Findings from the MAL-ED birth cohort study. *BMJ Global Health*, *3*, e000752. doi:10.1136/bmjgh-2018-000752

Martin, E. T., Fairchok, M. P., Stednick, Z. J., Kuypers, J., & Englund, J. A. (2013). Epidemiology of multiple respiratory viruses in childcare attendees. *Journal of Infectious Diseases*, *207*, 982–989. doi:10.1093/infdis/jis934

Moret, C., & Briley, M. (2011). The importance of norepinephrine in depression. *Neuropsychiatric Disease and Treatment*, *7*(Suppl 1), 9–13. doi:10.2147/NDT.S19619

Nankabirwa, J., Wandera, B., Kiwanuka, N., Staedke, S. G., Kamya, M. R., & Brooker, S. J. (2013). Asymptomatic plasmodium infection and cognition among primary schoolchildren in a high malaria transmission setting in Uganda. American *J*ournal of *T*ropical *M*edicine and *H*ygiene, *88*, 1102–1108. doi:10.4269/ajtmh.12-0633

Nawa, H., & Takei, N. (2006). Recent progress in animal modeling of immune inflammatory processes in schizophrenia: Implication of specific cytokines. *Neuroscience Research*, *56*, 2–13. doi:10.1016/j.neures.2006.06.002

Nokes, C., McGarvey, S. T., Shiue, L., Wu, G., Wu, H., Bundy, D. A., & Olds, G. R. (1999). Evidence for an improvement in cognitive function following treatment of *Schistosoma japonicum* infection in Chinese primary schoolchildren. *American Journal of Tropical Medicine and Hygiene*, *60*, 556–565. doi:10.4269/ajtmh.1999.60.556

Ohmit, S. E., & Monto, A. S. (2006). Symptomatic predictors of influenza virus positivity in children during the influenza season. *Journal of Biochemistry and Molecular Biology*, *43*, 564–568. doi:10.1086/506352

Pappas, D., Hendley, J., Hayden, F., & Winther, B. (2008). Symptom profile of common colds in school-aged children. *Pediatric Infection Disease Journal*, *27*, 8–11. doi:10.1097/INF.0b013e31814847d9

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences*, *31*, 464–468. doi:10.1016/j.tins.2008.06.006

Park, J., Lee, D., & Lee, Y. (2017). Relationship between high white blood cell count and insulin resistance (HOMA-IR) in Korean children and adolescents: Korean National Health and Nutrition Examination Survey 2008-2010. *Nutrition, Metabolism & Cardiovascular Diseases*, *27*(5), 456–461. doi:10.1016/j.numecd.2017.03.002

Patton, G. C., Sawyer, S. M., Santelli, J. S., Ross, D. A., Afifi, R., Allen, N. B., … M, R. (2016). Our future: A Lancet commission on adolescent health and wellbeing. *Lancet*, *387*, 2423–2478. doi:10.1016/S0140-6736(16)00579-1

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A., & Rohde, L. A. (2015). Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *Journal of Child Psychology and Psychiatry*, *56*, 345–365. doi:10.1111/jcpp.12381

Prince, M., Patel, V., Saxena, S., Maj, M., Maselko, J., Phillips, M. R., & Rahman, A. (2007). No health without mental health. *Lancet*, *370*, 859–877. doi:10.1016/S0140-6736(07)61238-0

Ramette, A., Spycher, B. D., Wang, J., Goutaki, M., Beardsmore, C. S., & Kuehni, C. E. (2018). Longitudinal associations between respiratory infections and asthma in young children. *American Journal of Epidemiology*, *187*, 1714–1720. doi:10.1093/aje/kwy053

Ratnayake, U., Quinn, T., Walker, D. W., & Dickinson, H. (2013). Cytokines and the neurodevelopmental basis of mental illness. *Frontiers in Neuroscience*, *7*, 180. doi:10.3389/fnins.2013.00180

Read, K., Settipani, C., Peterman, J., Kendall, P., Compton, S., Piacentini, J., … March, J. (2015). Predicting anxiety diagnoses and severity with the CBCL-A: Improvement relative to other CBCL scales? *J*ournal of *P*sychopathology and *B*ehavioral *A*ssessment, *37*, 100–111. doi:10.1007/s10862-014-9439-9

Robinson, S. L., Marin, C., Oliveros, H., Mora-Plazas, M., Richards, B. J., Lozoff, B., & Villamor, E. (2018). Iron deficiency, anemia, and low vitamin B-12 serostatus in middle childhood are associated with behavior problems in adolescent boys: Results from the Bogota school children cohort. *Journal of Nutrition*, *148*, 760–770. doi:10.1093/jn/nxy029

Rockx, B., De Wit, M., Vennema, H., Vinje, J., De Bruin, E., Van Duynhoven, Y., & Koopmans, M. (2002). Natural history of human calicivirus infection:

A prospective cohort study. *Journal of Biochemistry and Molecular Biology*, 246–253. doi:10.1086/341408

Roza, S. J., Hofstra, M. B., van der Ende, J., & Verhulst, F. C. (2003). Stable prediction of mood and anxiety disorders based on behavioral and emotional problems in childhood: A 14-year follow-up during childhood, adolescence, and young adulthood. *American Journal of Psychiatry*, *160*, 2116–2121. doi:10.1176/appi.ajp.160.12.2116

Singh, T., & Newman, A. B. (2011). Inflammatory markers in population studies of aging. *Ageing Research Reviews*, *10*(3), 319–329. doi:10.1016/j.arr.2010.11.002

Staat, M., Azimi, P., Berke, T., Roberts, N., Bernstein, D., Ward, R., … Matson, D. (2002). Clinical presentations of rotavirus infection among hospitalized children. *Pediatric Infectious Disease Journal*, *21*, 221–227. doi:10.1097/00006454-200203000-00012

Stanton, B., Clemens, J., Aziz, K., Khatun, K., Ahmed, S., & Khatun, J. (1987). Comparability of results obtained by two-week home maintained diarrhoeal calendar with two-week diarrhoeal recall. *International Journal of Epidemiology*, *16*, 595–601. doi:10.1093/ije/16.4.595

Stolzman, S., & Bement, M. H. (2012). Inflammatory Markers in Pediatric Obesity: Health and Physical Activity Implications. *ICAN: Infant, Child, & Adolescent Nutrition*, *4*(5), 297–302. doi:10.1177/1941406412459344

Tripathi, P. (2007). Nitric oxide and immune response. *Indian Journal of Biochemistry & Biophysics*, *44*, 310–319. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18341206

Tsapakis, E. M., & Travis, M. J. (2002). Glutamate and psychiatric disorders. *Advances in Psychiatric Treatment*, *8*, 189–197. doi:10.1192/apt.8.3.189

Van Praag, H. M. (1982). Depression, suicide and the metabolism of serotonin in the brain. *Journal of Affective Disorders*, *4*(4), 275–290. doi:10.1016/0165-0327(82)90025-8

von Stumm, S., Deary, I. J., Kivimaki, M., Jokela, M., Clark, H., & Batty, G. D. (2011). Childhood behavior problems and health at midlife: 35-year follow-up of a Scottish birth cohort. *Journal of Child Psychology and Psychiatry*, *52*, 992–1001. doi:10.1111/j.1469-7610.2011.02373.x

Watson, L., Little, P., Moore, M., Warner, G., & Williamson, I. (2001). Validation study of a diary for use in acute lower respiratory tract infection. *Family Practice*, *18*, 553–554. doi:10.1093/fampra/18.5.553

Webster, J. I., & Sternberg, E. M. (2004). Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products. *Journal of Endocrinology*, *181*(2), 207–221. doi:10.1677/joe.0.1810207

Wium-Andersen, M., Ørsted, D., Nielsen, S., & Nordestgaard, B. (2013). Elevated C-reactive protein levels, psychological distress, and depression in 73 131 individuals. *JAMA Psychiatry*, *70*, 176–184. doi:10.1001/2013.jamapsychiatry.102

Wright, J., Gundry, S., Conroy, R., Wood, D., Du Preez, M., Ferro-Luzzi, A., … Potgieter, N. (2006). Defining episodes of diarrhoea: Results from a three-country study in Sub-Saharan Africa. *Journal of Health, Population and Nutrition*, *24*, 8–16.