



Original Contribution

Childhood Infections and Adult Height in Monozygotic Twin Pairs

Amie E. Hwang, Thomas M. Mack, Ann S. Hamilton, W. James Gauderman, Leslie Bernstein, Myles G. Cockburn, John Zadnick, Kristin A. Rand, John L. Hopper, and Wendy Cozen*

* Correspondence to Dr. Wendy Cozen, Departments of Preventive Medicine and Pathology, USC Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, MC 9175, Los Angeles, CA 90089-9175 (e-mail: wcozen@usc.edu).

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Adult height is determined by genetics and childhood nutrition, but childhood infections may also play a role. Monozygotic twins are genetically matched and offer an advantage when identifying environmental determinants. In 2005–2007, we examined the association of childhood infections with adult height in 140 height-discordant monozygotic twin pairs from the California Twin Program. To obtain information on childhood infections and growth, we interviewed the mothers of monozygotic twins who differed in self-reported adult height by at least 1-inch (2.5 cm). Within-pair differences in the relative frequency of childhood infections were highly correlated, especially within age groups. A conditional logistic regression analysis demonstrated that more reported episodes of febrile illness occurred in the twin with shorter stature (odds ratio = 2.00, 95% confidence interval: 1.18, 3.40). The association was strongest for differences in the relative frequency of infection during the toddler years (ages 1–5: odds ratio = 3.34, 95% confidence interval: 1.47, 7.59) and was similar when restricted to twin pairs of equal birth length. The association was not explained by differential nutritional status. Measures of childhood infection were associated with height difference in monozygotic twin pairs, independent of genome, birth length, and available measures of diet.

body height; case-control studies; growth; infection; pediatrics; twins

Abbreviation: IGF-1, insulin-like growth factor 1.

Height, a fundamental biological characteristic of human beings, is linked to increased risk of multiple types of cancer (1–3) and is inversely associated with cardiovascular disease and stroke (4). Prospective cohort studies and meta-analyses examining height–disease relationships have found a consistent association between adult height and adult disease, even after adjustment for socioeconomic status, body mass index, menarche, and nutrition (1–3). Therefore, to completely understand the causes of human morbidity and mortality, it behooves us to fully understand the determinants of adult height.

Family studies (5) and studies of twins (6, 7), which assume that early environmental differences between monozygotic and dizygotic twins are similar in well-nourished and well-protected settings, have demonstrated that a large proportion of the variance in height is heritable. The environmental determinants accounting for the nonheritable

fraction of variance include both “common” (i.e., familial) and “unique” (i.e., personal) characteristics. Evidence from a study of 12,000 twin pairs suggests that the influence of “common” determinants decreases with age, but that the contribution of the “unique” environmental factors is consistent over age (6). One can speculate that nutritional factors are prominent among the former and individual-specific illnesses are among the latter.

In developing countries, children with infectious disease who experience arrested growth are concomitantly malnourished (8, 9). Nutritional deficiency increases susceptibility to infections and, conversely, episodes of infectious illness cause nutritional deficits by reducing intake, impairing nutrient metabolism and increasing energy expenditure (8, 10, 11). These mutual interactions are most likely responsible for dramatic changes in mean height that have occurred with periods of economic transition (12, 13).

However, the role of the individually more modest but universally much more frequent bouts of acute infection in the absence of malnutrition is unclear. It is biologically credible to postulate that the calories required for protection from, healing of, and recovery after acute infections necessarily detract from the reservoir of calories available for growth (14). Although easy to postulate, it is difficult to demonstrate such a relationship. The association between childhood infection and adult height has not been properly examined in the relative absence of variation in nutritional status. In addition, attempts to examine the question in a population in a nutritionally abundant setting must contend with the overwhelming influence of genetic determination. Ideally, assessment of the role of childhood infection on adult height requires a means of controlling both genetic and nutritional determinants.

Although the majority of monozygotic twin pairs achieve an identical height, a proportion of them are discordant. Because monozygotic twins completely share their genome, differences in their adult height are not due to heritable factors. Monozygotic twins in an economically developed society share early socioeconomic status and common access to the same food supply. They adopt a more similar diet than dizygotic twins (15, 16), even when raised apart (16), implying a heritable component to caloric intake. Thus, differences in height are likely to be at least partially determined by unique personal experiences such as illness, including infections.

Mothers of twins are accustomed to making within-pair comparisons and can report relative differences between paired monozygotic twins that are otherwise difficult to quantify (17). Accordingly, we have conducted a matched case-control comparison between the members of monozygotic pairs known to be discordant in height by at least 1 inch (2.5 cm). We confirmed the originally reported height difference and interviewed their mothers to assess the relative frequency of childhood infectious illnesses. We hypothesize that the twin who experienced more infections had shorter adult stature.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the USC Keck School of Medicine of the University of Southern California, and all subjects provided informed consent.

Participants

The subjects were monozygotic twins identified from the California Twin Program as characterized by their mothers. The California Twin Program is a population-based registry of twins born in California between 1908 and 1982 and is described in detail elsewhere (18). Briefly, twin pairs were identified from California birth records, and the twins' contact addresses were obtained by linkage to records of the California Department of Motor Vehicles during 1991–2000. In 2000, a 16-page screening questionnaire was sent to each twin, requesting information on demographic characteristics, zygosity, growth and development, reproductive

history, life-style factors, food frequencies, dietary preferences, and medical history. Roughly 45% of all such native resident twins independently completed and returned questionnaires.

In the California Twin Program questionnaire, each twin was asked to provide the height in inches and weight in pounds at the time of response, as well as at 18 years of age, for themselves and their twin and to provide the current height difference in inches.

A total of 305 monozygotic twin pairs (610 twins) born between 1968 and 1982 reported a height difference of at least 1 inch and were free of diabetes, rheumatoid arthritis, cancer, immunodeficiency, inflammatory bowel disease, and neurological disease, and, for females, initiated menarche within 6 months of each other. First contact with either twin enabled us to locate his or her co-twin, evaluate eligibility, verify the height difference, and contact and interview the mother (Web Figure 1 available at <http://aje.oxfordjournals.org/>). We located and contacted 378 twins, representing 176 pairs, and, of these, 349 twins (168 pairs) agreed to participate and allowed us to contact their mothers. Of the 168 mothers, 11 refused and 157 completed the interview; 17 mothers who could not identify the taller twin were excluded, yielding 140 mothers whose responses were the basis of the final analysis. Of these pairs, 73 were male and 67 female.

Exposure assessment

A 30-minute interview was conducted with each mother about her twins' medical history, puberty markers, and physical development. By using a case-control design, the shorter member of the pair was designated as the "case" and the taller, the "control." Each mother was asked about each twin's experience with febrile illnesses, physician visits, ear infections, antibiotic use, frequency of missed day care and school due to febrile illness, and the frequency with which she herself missed work due to each twin's illness. Each question was repeated for 5 age-specific periods: infancy (<1 year), toddlerhood (1–5 years), elementary school years (6–10 years), adolescence (11–13 years), and teenage years (14–18 years). She was asked about each twin's history of infectious mononucleosis, persistent cough, and flu during the teenage years. Additionally, she was asked to quantify the overall frequency of tonsillitis, stomach flu, and diarrhea, as well as the frequency of participation in sports before age 13 for each twin. Information on the twins' relative birth weight, birth length, and weight and height at ages 6, 10, 13, and 18 was also obtained. The within-pair difference in growth rate was crudely assessed by indicating which twin grew faster during each of the 5 age periods.

A random sample of 51 mothers was recontacted 4 years later for additional information, including the twins' childhood medical history of fractures and their comparative dietary intake (i.e., which twin ate larger food portions). Each was asked to reconfirm the twins' length and weight at birth from available records and for her personal opinion about the reasons for the adult height difference.

Each question was framed as a within-pair relative ranking (which twin was sick more often?), as well as an

individual frequency-based measure (how often was each twin sick?) using broad ordinal categories (never, rarely, sometimes, and frequently). For either form of response, a scoring system was used to summarize the twins' illness experience. The twin with greater exposure (i.e., more febrile illness, missed school more often, etc.) was given a score of 1 for each individual exposure, and the other twin was given a score of 0. When exposures were reported to be similar in both twins, both were given a score of 0.

To evaluate whether differences in nutrition contributed to the height difference, a comparison of nutritional intake based on the original California Twin Program questionnaire was performed. From the set of 43 food frequency and 127 food preference items, representative growth-pertinent foods (beef/lamb, bread, broccoli/spinach/greens, milk, and cheese/yogurt/ice cream) were selected. For a given food, each twin chose from 7 food frequency choices (from 0 to ≥ 15 times per week), indicated which twin had regularly consumed that food more frequently, and indicated his/her preference by responding to these questions: "Do you dislike [the specific food] a lot, dislike it, take it or leave it, like it, or like it a lot?", scored 0–4 in that sequence.

Statistical analysis

To assess independence of the reported within-pair differences in infection frequency, we performed a Spearman correlation analysis and principal component analysis using the principal axis method to extract the components by orthogonal rotation. Conditional logistic regression modeling adjusting for birth length and weight was used to test the hypothesis that more frequent illness was associated with shorter stature, and a stepwise model selection process was used to determine the most predictive exposure (within-pair difference). In order to characterize the association between exposure variables and determine heterogeneity across age categories, we used χ^2 tests of heterogeneity.

To address possible misclassified height differences and to assess dose-response, we conducted a stratified analysis by the degree of difference (1 inch vs. >1 inch) and performed a test for interaction between groups defined by adult height difference (1 inch vs. >1 inch) and gender.

In order to examine the associations independent of birth length, we repeated the analysis stratified by relative birth length and performed tests for interaction between relative differences in birth length and in the frequency of early life illness, and we examined the relationship between length and weight at birth and the exposures of interest. The independent variables in these analyses were the relative difference in birth length and weight, and the dependent variables were within-pair differences in infection frequency by age. The likelihood ratio χ^2 test was used to test the overall association, and the effect was estimated by using an odds ratio, calculated by fitting the conditional logistic regression models. The effects of birth length, birth weight, and growth at ages 6, 10, 13, and 18 years on adult height were similarly examined, adjusting for body size at each previous age.

To assess diet as a possible confounder, we examined the responses to dietary questions at ages 18–32 years. Those for the "case" (shorter twin) were compared with those for

the "control" (taller twin) by using a paired *t* test (food frequency) or a paired signed-rank test (food preference, intra-pair comparison). For each twin, the body mass index at age 18 years was calculated on the basis of the twin's own responses from the original California Twin Program responses.

All odds ratios are reported with 95% confidence interval. If the number of exposure-discordant pairs was less than 5, a Fisher's exact test was used to calculate an exact odds ratio and 95% confidence interval for logistic regression analyses. *P* values are reported for tests of interaction and likelihood ratio χ^2 tests. Statistical analysis was performed by using SAS, version 9.2, software (SAS institute, Inc., Cary, North Carolina).

RESULTS

The subjects were largely European American, corresponding to the reference population of each corresponding California birth cohort (Table 1).

The relative differences in the frequency of childhood illness were significantly correlated (Web Tables 1 and 2). The Spearman correlation coefficients were generally higher within a given age group (Web Table 1) than across age groups (Web Table 2). When examined across all 5 age groups, the correlation coefficients decreased as the age interval increased. By principal component analysis, measures of within-pair differences in illness frequency tended to cluster by age category, resulting in 1 component each for infancy, toddler years, elementary school years, adolescence, and teenage years (data not shown).

The twin with more maternally reported episodes of childhood infection was approximately twice as likely to be the shorter twin (Table 2). This was evident for each measure of illness frequency and persisted after adjustment for birth weight and birth length (Table 2; Web Figure 2). There were no statistically significant differences in the odds ratios among the 5 age categories (χ^2 test of heterogeneity not shown). In a stepwise model, the within-pair difference in febrile illness frequency during the toddler years was the strongest and most significant predictor of adult height difference (data not shown). Moreover, within-pair differences in illness during toddlerhood were generally associated with slightly higher odds ratios, ranging from 1.96 for more antibiotic use to 4.67 for more days of missed school, as well as narrower 95% confidence intervals (Table 2), than other estimates at other ages. When the analysis was restricted to pairs with the same birth length, the effect estimates were slightly higher, although less precise due to smaller sample size (Table 2). For example, within this subset, the twin with more reported antibiotic use was 3 times as likely to become the shorter twin of the pair. We found no evidence of interaction between birth length and relative illness on stature (data not shown).

The association between more toddler infections and shorter stature was stronger among the subset of pairs differing by more than 1 inch compared with the subset differing by just 1 inch, although no longer significant (Web Table 3). Gender did not modify the association between infection frequency and adult height difference (data not shown).

Table 1. The Demographic Distribution of Monozygotic Twin Pairs Discordant for Adult Height, California, 2005–2007

	Study Twin Pairs ^a				All Eligible Twin Pairs ^b		All CTP Twin Pairs ^c	
	No. of Pairs	%	Mean (SD)	Mean (Range)	No. of Pairs	%	No. of Pairs	%
Total	140				305		7,249	
Gender								
Male-male	73	52.1			148	48.5	1,803	24.9
Female-female	67	47.9			157	51.5	3,937	54.3
Male-female							1,509	20.8
Ethnicity								
White	111	79.3			227	74.4	5,659	78.1
Black	5	3.6			15	4.9	198	2.7
Latino	12	8.6			34	11.1	860	11.9
Asian	5	3.6			17	5.6	264	3.6
Other	7	5.0			12	3.9	268	3.7
Height of case twins (inches ^d)								
Male			70.1 (3.0)					
Female			64.6 (2.6)					
Height of control twins (inches ^d)								
Male			71.1 (3.3)					
Female			65.6 (2.6)					
Height difference (inches ^d)				1.1 (0.25–4)				
Mothers' age at participation, years				58 (42–72)				
Twins' age at mothers' participation, years				31 (22–39)				

Abbreviations: CTP, California Twin Program; SD, standard deviation.

^a Twin pairs whose mothers' responses contributed to this study.

^b Double responding monozygotic twin pairs from CTP born between 1968 and 1982 who were discordant in height by at least 1 inch and free of diabetes, rheumatoid arthritis, cancer, immunodeficiency, and neurological diseases.

^c Double responding twins from CTP born between 1968 and 1982.

^d One inch = 2.5 cm.

As expected, body size differences in early life were robustly associated with adult height differences (Web Table 4). Shorter height at 6, 10, 13, and 18 years of age was more strongly associated with shorter adult height than was weight at each age. Shorter height at age 6 years was most strongly predictive of shorter adult height (odds ratio = 27.4; ratio of exposure-discordant twin pairs = 89/3); 41% of the taller and 40% of the shorter twins reported that the disparity in height had appeared before age 6; 58% and 56%, respectively, indicated that it had appeared before the age of 12 years. After adjustment for birth weight, the twin who was shorter at birth was more likely to experience more frequent illness (Table 3), but differences in birth weight were not associated with illness after adjustment for birth length (Table 3).

Ten of the 51 recontacted mothers were able to check the previously reported differential length and weight at birth from hospital records or birth certificates; 9 confirmed their earlier reports. Forty of the 41 remaining mothers subjectively confirmed their original estimates. When asked what

contributed to their twins' height difference, none of the mothers suspected a role for childhood illness.

Only 1 mother reported that a twin with a leg fracture, and that had occurred in the taller co-twin. Over 80% of the 51 mothers could describe no consistent differences in the childhood diet of their height-discordant twins, and the differences reported by the other 20% were not correlated with the height disparity. Neither food intake, nor food preference, nor relative consumption of any food as young adults was associated with height (Web Table 5).

DISCUSSION

The twin with more maternally reported episodes of childhood illness was approximately 2 times as likely to be the shorter twin. Because most questions to mothers were related to infections, (e.g., frequency of antibiotic use and febrile illness), and since those with chronic disease had been excluded, infections probably accounted for the majority of reported illnesses. The association was strongest for

Table 2. The Effect of the Relative Difference in Childhood Illness Frequency on Shorter Stature in Monozygotic Twin Pairs Discordant for Adult Height^a, California, 2005–2007

Exposures	All Ages (0–18 Years)						Toddler Years (1–5 Years)			
	No. of Infectious Exposure-Discordant Twin Pairs		OR _{crude}	95% CI	OR _{adjusted} ^b	95% CI	No. of Infectious Exposure-Discordant Twin Pairs		OR _{adjusted} ^b	95% CI
	Case ^c Exposed	Control ^d Exposed					Case ^c Exposed	Control ^d Exposed		
All twins (140 pairs)										
More febrile illnesses	59	26	2.27	1.43, 3.60	2.00	1.18, 3.40	38	11	3.34	1.47, 7.59
More physician visits	56	27	2.07	1.31, 3.28	1.89	1.10, 3.26	32	13	2.46	1.11, 5.46
More antibiotic use	51	26	1.96	1.22, 3.15	1.80	1.04, 3.13	34	15	1.96	0.95, 4.01
More school missed because of illnesses	32	20	1.60	0.92, 2.80	1.80	0.91, 3.58	14	4	4.67	1.13, 19.22
Similar birth length (68 pairs)										
More febrile illnesses	28	11	2.55	1.27, 5.11	2.95	1.34, 6.48	12	5	3.21	0.86, 15.38
More physician visits	24	15	1.60	0.84, 3.05	2.18	1.00, 4.74	10	5	3.66	0.90, 19.12
More antibiotic use	22	10	2.20	1.04, 4.65	3.30	1.34, 8.09	11	6	2.45	0.79, 7.63
More school missed because of illnesses	15	6	2.50	0.97, 6.44	4.45	1.36, 14.54	5	1	45.90	0.91, 1,000

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Discordant for adult height by at least 1 inch (2.5 cm).

^b Adjusted for birth weight and birth length.

^c Case twin is the shorter twin of the pair.

^d Control twin is the taller twin of the pair.

infections during the toddler years, when the difference in height usually appeared, and was independent of birth length and weight. In this study of monozygotic twins, the association between illness in the early years and adult height was independent of heritable factors, childhood social class, and parental behavior.

Twins had to be located in order to enroll their mothers. Of the 176 located families, 8 twin pairs and 11 mothers were unwilling to participate, an overall compliance of 95% for the twins and 93% for the mothers. Concerns of selection bias might be raised because the time required to locate more families was not available. However, young adulthood is the most mobile period of American life (19), and difficulties in locating young adult twins, roughly a decade after last contact, are to be expected because of geographic dispersion and changes in telephone access. Only if the cases and controls were separately ascertained would such a loss produce selection bias. In this study, whether the taller or shorter twin was first located, the other followed, and therefore no differential selection was based on height or illness because pairs were either included or excluded as a unit. Only an

inadequate sample size and/or the introduction by chance of nondifferential misclassification would constitute cause for concern based on statistical power, not selection bias. The power proved sufficient, although chance could, as always, have produced a random distortion in the selection of pairs.

More important limitations of our study include potential information bias with respect to height not validated by direct measurement, maternal recollection of length and weight at birth and of relative differences in the frequency of illness, and the possibility of confounding by nutritional status, a known determinant of height.

A study of Australian twin pairs found that young adult twins accurately report height, although shorter individuals tend to slightly overestimate and taller individuals tend to slightly underestimate (20). If such misclassification occurred in our study, it would have resulted in underestimation of the average height differences, suggesting that the measured associations were slightly underestimated.

Although numbers are small, the available medical records confirmed 90% of the mother's initial reports, and 98% of the mothers consistently reported the same birth size

Table 3. The Effect of Smaller Birth Size on the Relative Frequency of Illness in Toddler Years (1–5 Years) and Childhood (0–18 Years) in Monozygotic Twin Pairs Discordant for Adult Height, California, 2005–2007

Exposures	More Febrile Illnesses					More Physician Visits					More Antibiotic Use					More Missed School Because of Illnesses				
	No. of Infectious Exposure-Discordant Twin Pairs		OR _{crude}	OR _{adjusted} ^a	P Value ^b	No. of Infectious Exposure-Discordant Twin Pairs		OR _{crude}	OR _{adjusted} ^a	P Value ^b	No. of Infectious Exposure-Discordant Twin Pairs		OR _{crude}	OR _{adjusted} ^a	P Value ^b	No. of Infectious Exposure-Discordant Twin Pairs		OR _{crude}	OR _{adjusted} ^a	P Value ^b
	Case ^c Exposed	Control ^d Exposed				Case ^c Exposed	Control ^d Exposed				Case ^c Exposed	Control ^d Exposed				Case ^c Exposed	Control ^d Exposed			
Toddler years																				
Shorter birth length	28	8	3.5*	4.1*	0.05	23	10	2.3*	3.4*	0.14	25	10	2.5*	2.3	0.16	11	5	2.2	2.5	0.05
Lower birth weight	28	19	1.5	0.8	0.77	24	19	1.3	0.6	0.70	30	17	1.8	1.1	0.51	10	7	1.4	0.9	0.76
Childhood																				
Shorter birth length	41	14	2.9*	3.2*	0.04	39	13	3.0*	4.6*	0.06	37	15	2.5*	3.0*	0.004	23	14	1.6	3.0*	0.09
Lower birth weight	48	32	1.5	0.9	0.33	44	34	1.3	0.6	0.95	42	29	1.5	0.8	0.54	24	25	0.9	0.5	0.90

Abbreviation: OR, odds ratio.

* $P < 0.05$.^a Adjusted for birth weight and birth length.^b Two-sided P values for test of overall association between illness in early years and birth size by using the likelihood ratio χ^2 test.^c Number of twin pairs in which the case (shorter twin) is exposed, and the control (taller twin) is unexposed.^d Number of twin pairs in which the case (shorter twin) is unexposed, and the control (taller twin) is exposed.

difference. Although relative and subjective measures of illness frequency were not confirmed by medical records, mothers' reports have been shown to be highly reliable and consistent and a credible data source (21–23). Medical record validation was infeasible, even had physicians been consulted for each illness (24), because documentation would probably not have been sufficiently thorough.

Twins and their mothers commonly make comparisons, especially between childhood experiences, and monozygotic twins tend to agree about existing qualitative differences in developmental milestones (17). The consistently high and significant associations between relative height and the within-pair differences in frequency of physician visits, relative use of antibiotics, and the relative occurrence of febrile illness also support the validity of the reported information.

Mothers might report more frequent illnesses in the shorter compared with taller twin. However, we asked the twins at recruitment and mothers at follow-up what they believed caused the difference in twins' height. None of these twins had experienced a prolonged illness episode in childhood, and neither a single pair of twins nor a single mother suspected that childhood illness might be related to the height disparity.

Because height is influenced by nutrition, particular scrutiny for confounding by cumulative nutrition is important. Diet is influenced by genetic factors, and monozygotic twins repeatedly have been shown to be similar in nutritional status (15, 16). These height-discordant twins, in the view of their mothers, had similar diets as children. According to the young adult twins themselves, the most sensitive observers of between-twin differences, their food preferences, habits, and levels of obesity were nearly identical at the time of contact and are unlikely to have changed since childhood (15, 25). Thus, the available evidence suggests that the relative frequency of infections may be independently associated with adult height.

If causal, several possible mechanisms could explain the association. Infections during early childhood result in periods of catabolism, diverting calories away from growth (14). Immune cells require energy to maintain routine house-keeping functions and to maintain specific responses to infections, that is, lymphocyte expansion and protein production (cytokines, cell surface proteins, and enzymes) (26). Compared with quiescent immune cells, activated immune cells require 40% additional energy in the form of adenosine triphosphate (26). The fever associated with infection results in a 13% increase in metabolic rate per centigrade degree of fever (27). Respiratory infections and diarrhea both produce a reduction in food intake by 20% (10), promoting a negative energy balance. Early childhood years are immunologically and developmentally demanding periods during which physical growth occurs at its highest velocity with a substantial proliferation of T and B cells (14). Because the balance between energy allocated for immune function and growth must be carefully maintained (14), ill children may spend their energy fighting infection instead of increasing long bone length, resulting in shorter adult height. Moreover, inflammatory responses may affect production of growth hormone and insulin-like growth factor 1 (IGF-1), both of

which are critical to long bone growth. Growth hormone and IGF-1 promote cell division and differentiation at the level of the growth plate (28, 29). During infections, there is increased production of proinflammatory cytokines interleukin 6, tumor necrosis factor α , and interleukin 1 β (30–32), thought to mediate decreases in IGF-1 and growth hormone (29, 33). Interleukin 6, tumor necrosis factor α , and interleukin 1 β also inhibit growth plate chondrocyte differentiation (29); hence, chronic exposure to inflammation can delay growth (33, 34).

We report that childhood infection is significantly associated with height differences in monozygotic twins, independent of genetics, socioeconomic status, parental behavior, and available indicators of nutrition. Although the relationship between childhood infections and growth has been studied extensively in developing countries, our results also suggest a relationship between childhood infections and adult height in a generally healthy, economically developed population.

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