

The association of low birth weight with serum C reactive protein in 3-year-old children living in Cuba: A population-based prospective study

Silvia Josefina Venero-Fernández¹ | Hermes Fundora-Hernández¹ |
 Lourdes Batista-Gutierrez¹ | Ramón Suárez-Medina¹ | Esperanza de la C. Mora-Faife¹ |
 Gladys García-García¹ | Ileana del Valle-Infante¹ | Liem Gómez-Marrero¹ |
 John Britton² | Andrew W. Fogarty² | and the
 HINASIC (Historia Natural de la Sibilancia en Cuba/Natural History of Wheezing in Cuba)
 Study Group

¹Instituto Nacional de Higiene, Epidemiología y Microbiología, Infanta No 1158 e/ Llinás y Clavel, Código Postal 10300, La Habana, Cuba

²Nottingham Biomedical Research Unit, Division of Epidemiology and Public Health, University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham, NG5 1PB, United Kingdom

Correspondence

Silvia Josefina Venero-Fernández, Infanta No 1158 e/Llinás y Clavel, Código Postal 10300, La Habana, Cuba.
 Email: silviavf@inhem.sld.cu

Abstract

Objective: Low birthweight is associated with a decreased risk of childhood leukemia and an increased risk of both cardiovascular disease and all-cause mortality in adult life. Possible biological mediators include systemic innate immunity and inflammation. We tested the hypothesis that birthweight was inversely associated with serum high sensitivity C reactive protein assay (hsCRP), a measure of both innate immunity and systemic inflammation.

Methods: Data on birthweight and current anthropometric measures along with a range of exposures were collected at 1 and 3 years of age in a population-based cohort study of young children living in Havana, Cuba. A total of 986 children aged 3-years-old provided blood samples that were analyzed for serum hsCRP levels.

Results: Nearly 49% of children had detectable hsCRP levels in their serum. Lower birthweight was linearly associated with the natural log of hsCRP levels (beta coefficient -0.70 mg L^{-1} per kg increase in birthweight, 95% CI: -1.34 to -0.06). This was attenuated but still present after adjustment for the child's sex and municipality (-0.65 mg L^{-1} per kg birthweight; 95% CI: -1.38 to $+0.08$). There were no associations between growth from birth or anthropometric measures at 3 years and systemic inflammation.

Conclusions: Birthweight was inversely associated with serum hsCRP levels in children aged 3 years living in Cuba. These observations provide a potential mechanism that is present at the age of 3 years to explain the association between low birthweight and both decreased childhood leukemia and increased cardiovascular disease in adults.

KEYWORDS

birthweight, children, Cuba, inflammation

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2016 The Authors American Journal of Human Biology Published by Wiley Periodicals, Inc.

1 | INTRODUCTION

Exposures from conception onwards are well recognized to impact birthweight and subsequent diseases in adulthood (Gluckman et al., 2008). The associations between lower birthweight and decreased risk of childhood leukemia (Belson et al., 2007; Hjalgrim et al., 2004; Paltiel et al., 2004) and increased cardiovascular disease (Huxley et al., 2007; Mu et al., 2012; Risnes et al., 2011) and all-cause mortality (Risnes et al., 2011) in adults are well recognized although the pathogenetic mechanisms are unclear. Potential biological processes that may be on the casual pathway for these observations include innate immunity whereby immune surveillance prevents the development of aberrant cells into clinical malignancies (Bindea et al., 2010; Chow et al., 2011; Ostrand-Rosenberg, 2008), and systemic inflammation, which is known to be a risk factor for cardiovascular disease (Danesh et al., 2000; Ridker and Cook, 2004; Ridker et al., 1998, 2000). High sensitivity C reactive protein (hsCRP) is a member of the pentraxin protein family, and is a biomarker that contributes to both innate immunity (Du Clos and Mold, 2004; Simons et al., 2014) and also systemic inflammation (Black et al., 2004; Mortensen, 2001), and is positively associated with higher all-cause mortality in adults (Zacho et al., 2010). Prospective studies in children may increase understanding of these associations by determining if birthweight is associated with increased hsCRP levels in later childhood.

Cuba has an excellent health care system that delivers infant mortality rates comparable to much richer countries (Cooper et al., 2006), with good health infrastructure providing a unique environment where risk factors for disease can be studied. We have used data from a prospective study in young children to test the primary hypothesis that low birth weight is associated with increased hsCRP levels at the age of 3 years.

2 | MATERIALS AND METHODS

2.1 | Study population and setting

The study design is a prospective observational epidemiological study. All children aged between 12 and 15 months who were living in Havana, Cuba, between March 2010 and March 2011 and who attended one of 17 policlinics, nested in four municipalities in Havana, Cuba, were eligible to be randomly selected to participate in the study (Arroyo Naranjo, Cerro, Habana del Este, La Lisa). Recruitment for the study (Appendix) has been described in detail elsewhere (Venero-Fernandez et al., 2013). The study protocol was approved by the local Havana Scientific Committee in Cuba

and also by the University of Nottingham Medical School Ethics Committee in the United Kingdom.

2.2 | Data collection

The study was initially designed to identify environmental exposures that may increase the risk of asthma or allergic disease in Cuba (Fundora Hernández et al., 2014; Suarez-Medina et al., 2014; Venero-Fernandez et al., 2013). The baseline data collection in eligible children at the age of 1 year consisted of an interviewer-administered questionnaire that collated the responses from the parent/caregiver about prenatal and postnatal exposures of the child, their living environment, and the medical history of the family. Birthweight was obtained from the child's medical records of the readings taken at the place of birth. Specific questions focused on smoking history, including that of the mother during pregnancy, and also information on exposure to individuals who smoke tobacco in the infant's home. The children and their caregivers were resurveyed 2 years later when the children were ~3-years-old and clinically stable. Data on the height and weight at the time of the interview were also collected using the measuring equipment and weighting scales available in the policlinic which were calibrated every 6 months by the Ministry of Health. For those 3-year-old children whose parents gave consent, a blood sample was taken. This was frozen and subsequently analyzed for serum hsCRP using an immunoturbidimetric assay (SpinReact, Spain) on a SpinLab 100 (SpinReact, Spain) analyzer in a standardized manner designed to minimize measurement error (Spinreact high sensitivity CRP assay).

2.3 | Data analysis

The data were entered into an electronic database, cleaned, and checked for errors. All statistical analyses were carried out in Stata v14 (StataCorp, Texas) using the survey commands (svyset) to allow for the clustered survey design (Stata Corp). The distribution of serum hsCRP levels was transformed into natural logarithms after adding +0.00001 to accommodate undetectable values.

Linear regression analyses were then performed using logCRP at the age of 3 years as the primary endpoint and birthweight as the main independent variable. The associations of weight at 3 years and change in weight since birth with logCRP were secondary endpoints. A number of further exposures were added to the model in a stepwise manner and they were retained if they changed the size of statistically significant associations by 10% or more. These were municipality, sex, duration of exclusive breastfeeding (categorical), mother smoking in pregnancy, presence of smokers in the household at 1 year and at 3 years of age (categorical), self-reported pollution in their locality at age 1 year and at 3

TABLE 1 Characteristics of study participants

Variable	Definition of category	All children: N = 1543	Children who did not give blood N = 557	Children who gave blood N = 986
Mean age in years (range)		3 (3–3)	3 (3–3)	3 (3–3)
Skin color (%)	White	695 (45)	256 (46)	439 (45)
	Mixed	652 (42)	238 (43)	414 (42)
	Black	196 (13)	63 (11)	133 (13)
Gender (%)	Female	753 (49)	278 (50)	475 (48)
	Male	790 (51)	279 (50)	511 (52)
Municipality (%)	Habana Este	480 (31)	135 (24)	345 (35)
	Cerro	229 (15)	88 (16)	141 (14)
	La Lisa	264 (17)	204 (37)	60 (6)
	Arroyo Naranjo	570 (37)	130 (23)	440 (45)
Median number of siblings (IQR)	–	1 (0–2)	1 (0–1)	1 (0–2)
Median duration of breastfeeding, months, (IQR)		4 (2–5)	4 (2–5)	4 (2–5)
Mean age of mother at birth in years (sd)	–	26.7 (6.2)	26.2 (6.2)	26.9 (6.2)
		N = 1542		N = 985
Mothers education	Primary	26 (2)	11 (2)	15 (2)
	Secondary	417 (27)	162 (29)	255 (26)
	Pre-University	895 (58)	305 (55)	590 (60)
	University	205 (13)	79 (14)	126 (13)
Smokers living in home at 1 year	No	726 (47)	258 (46)	468 (47)
	Yes	817 (53)	299 (54)	518 (53)
Smokers living in home at 3 years	No	742 (48)	267 (48)	475 (48)
	Yes	801 (52)	290 (52)	511 (52)
Self-reported pollution at home at 1 year	Yes	1126 (73)	423 (76)	703 (71)
	No	417 (27)	134 (24)	283 (29)
Self-reported pollution at home in 3 years	Yes	1058 (69)	376 (68)	682 (69)
	No	485 (31)	181 (32)	304 (31)
Birthweight, kg (sd)	–	3.32 (0.52)	3.31 (0.52)	3.33 (0.52)
		N = 1540	N = 556	N = 984
Weight at 3 years, kg (sd)	–	15.83 (2.58)	15.66 (2.62)	15.93 (2.55)
Height at year 3, m (sd)	–	0.96 (0.07)	0.95 (0.07)	0.96 (0.07)

IQR = interquartile range.

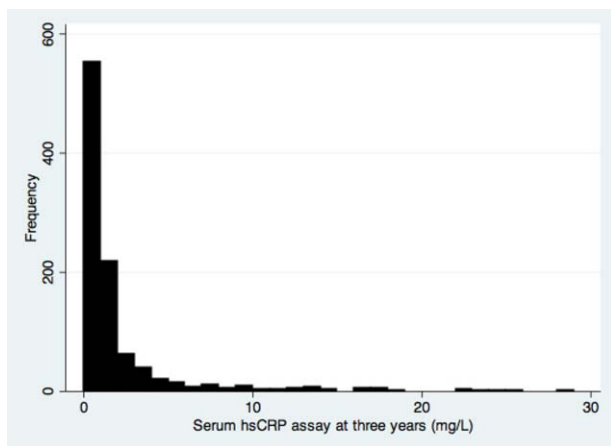


FIGURE 1 Distribution of serum hsCRP levels in study population

years of age, mother's age (categorical), number of siblings (categorical) and maternal education (categorical). Interactions were explored for sex using the likelihood ratio testing with a P value of <0.10 as evidence of an interaction. To explore the possibility of subclinical infections driving higher levels of serum hsCRP, sensitivity analyses were implemented restricting the study population to those with an hsCRP level of less than either 10 or 20 mg L^{-1} . Assumptions of linearity were tested by comparing the linear model with the categorical model using likelihood ratio tests.

3 | RESULTS

Of the 3-year-old 1,543 children who participated in the survey, 986 (64%) provided blood samples for analysis of serum CRP levels. Children who provided blood were similar to those who did not in terms of birthweight, but were slightly more likely to live in the Habana del Este and Arroyo Naranjo municipalities than those who did not contribute blood samples (Table 1). Forty-nine percent of children who provided blood samples had a detectable serum

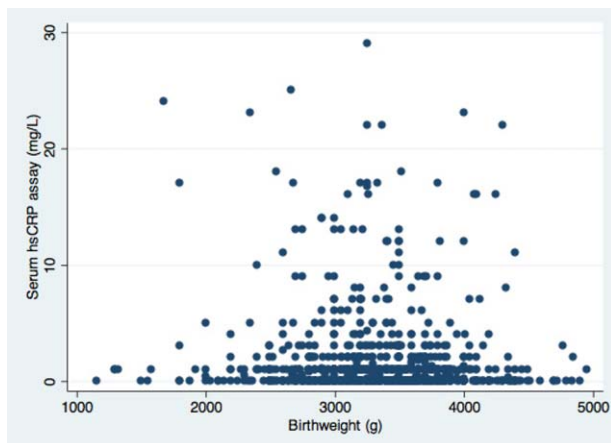


FIGURE 2 Scatter graph of the association between serum high sensitivity CRP levels and birthweight

CRP level and the distribution is presented in Figure 1, with a lowest detectable value of 0.01 mg L^{-1} . The association with birthweight presented in Figure 2.

In the primary analysis of the association between birthweight and log serum hsCRP levels at age 3 years (Table 2), there was a significant linear association in the univariate analysis ($-0.70 \text{ mg L}^{-1} \text{ kg}^{-1}$ birthweight, 95% confidence intervals CI: -1.34 to -0.06). There was no effect modification of this association by sex. These associations persisted in sensitivity analyses restricting the population to those with serum hsCRP measurements $<20 \text{ mg L}^{-1}$ ($-0.65 \text{ mg L}^{-1} \text{ kg}^{-1}$; 95% CI: -1.37 to $+0.78$) and $<10 \text{ mg L}^{-1}$ ($-0.59 \text{ mg L}^{-1} \text{ kg}^{-1}$; 95%CI: -1.31 to $+0.14$).

Both place of location (municipality) and the child's sex were significant confounding factors (Table 2). Adding both of these variables to the model gave a similar association as seen in the univariate model ($-0.65 \text{ mg L}^{-1} \text{ kg}^{-1}$; 95% CI: -1.38 to $+0.08$, $P = 0.07$). Repeating the univariate analysis with no adjustment for sampling gave a similar qualitative association with wider confidence intervals between the highest category of serum hsCRP levels and birthweight ($-0.70 \text{ mg L}^{-1} \text{ kg}^{-1}$, 95%CI: -1.56 to $+0.16$).

There were no significant associations between CRP levels at the age of 3 years and either weight at 3 years, body mass index at 3 years, height at 3 years or change in weight at 3 years from birth. Similarly, there was no association with either the presence of smokers in the house at age 3 years or the duration of exclusive breastfeeding with logCRP levels.

4 | DISCUSSION

To our knowledge this is the largest prospective population-based study to investigate the association between birthweight and serum hsCRP levels in 3-year-old children. Our data demonstrate that birthweight is inversely associated with serum hsCRP measurements at 3 years, with a one kg increase in weight associated with an $\sim 50\%$ decrease in serum hsCRP. These associations have potential implications for understanding how low birthweight is associated with disease in later life.

The strengths of our data include the randomly selected prospective population-based study from which these children were recruited and the detailed phenotypic information collected on a number of environmental exposures from pregnancy onwards, allowing consideration of potential confounding or causal exposures. The data on birthweight were collected from medical records obtained as part of the infant's postnatal care, giving confidence that these data are not influenced by recall bias. Subsequent data on weight and height at the age of 3 years were also collected at the polyclinic using validated medical equipment. The blood samples

were collected, processed and stored in a standardized manner and then analyzed in batches in a central laboratory, providing confidence in the integrity of these data. The persistence of the associations after sensitivity analyses restricted to lower levels of serum hsCRP suggests that these observations are robust.

Although we were only able to collect blood samples for analysis from 64% of those who attended, significant selection bias is unlikely as those who did provide blood were generally similar to those who did not. The blood samples were collected in the early morning through the year in a tropical country and hence temperature and ambient pollution may be expected to vary according to season and weather conditions. We are unable to adjust for these factors, but anticipate that they are most likely to generate a non-systemic measurement error in CRP values that would not bias our observations. Similarly, although we only recruited individuals with no current symptoms of infection, we were unable to exclude infection at the time of blood collection; again this would be expected to lead to non-systemic measurement error, and hence would be unlikely to bias our observations unless low birthweight increased susceptibility to infection and hence prevalence of subclinical infection.

There are no existing population-based studies of the association between birthweight and serum hsCRP levels in young children that we are aware of. One study from the UK in 553 children aged 10–11 years reported a median hsCRP value of 0.15 mg L^{-1} and no association with birthweight either before or after adjustment for current body size (Cook et al., 2000). An analysis of 996 Mexican American children aged 6–11 years who provided data for the Third National Health and Nutrition Survey in 1988–1994 in the USA reported that 11% of children had CRP values of 2.1 mg L^{-1} or more, and that again there was no association with birthweight in this population (Gillum, 2003). One limitation of the second study is the unavailability of the high sensitivity CRP assay that precludes direct comparison with our study population. However, the aforementioned two studies in children aged 6–11 years did report a positive association between body habitus and serum CRP, which was not present in our larger dataset. It is possible that the mechanism that drives the well recognized association between adiposity and serum hsCRP (Fogarty et al., 2008) is not established at the age of 3 years.

Other studies of the association between birthweight and CRP levels have been in adults and these studies are probably more susceptible to confounding by environmental factors as the participants will have had more time to accumulate exposures. In particular, it is unclear if current body fat is on the causal pathway or may be considered a confounding factor. The potential importance of confounding by adiposity is reflected in the fact that the majority of stud-

ies of the association between birthweight and CRP in adults only observed an association after adjustment for body habitus. The MIDSPAN family study reported no initial association between serum hsCRP and birth weight in preliminary analyses in 1663 individuals aged 30–59 years, but after adjustment for body mass index an inverse linear association between serum hsCRP and birth weight was observed, with a 10.7% decrease in hsCRP for each 1kg increase in birth weight (Sattar et al., 2004). Data from the Bogalusa Heart Study similarly reported an inverse linear association between hsCRP in 776 adults aged 24–43 years after adjusting for the confounding factors that included BMI (Bhuiyan et al., 2011). Data from 1461 participants from a birth cohort in the Philippines who were aged 21 years found no initial association between birthweight and serum CRP in tertiles in initial analyses, but a negative association was observed after adjustment for a number of confounding factors including current waist circumference and skinfold thickness (McDade et al., 2010). Data from a birth cohort from Finland of 5840 participants aged 31 years, observed that hsCRP levels were 16% higher for each 1 kg decrease in birth weight after adjustment for body mass index, and 6% higher without adjustment for BMI (Tzoulaki et al., 2008). Analysis of data from the US National Longitudinal Study of Adolescent Health reported that, at the age of 24–32 years, the association between birth weight and serum hsCRP was non-linear, being positive for birth weights $<2.8 \text{ kg}$ and above this threshold the association was negative (McDade et al., 2014).

The observation that low birthweight is associated with higher levels of cardiovascular disease (Huxley et al., 2007; Mu et al., 2012; Risnes et al., 2011) and all-cause mortality in adults is well recognized. The association of higher birthweight with childhood leukemia also has been the topic of a number of studies (Belson et al., 2007; Hjalgrim et al., 2004; Paltiel et al., 2004). Our observations that low birthweight is associated with higher circulating hsCRP levels at the age of 3 years do not demonstrate that this is the biological mechanism that explains these observations. However, it does permit us to speculate that via its role in contributing to innate immunity (Du Clos and Mold, 2004; Simons et al., 2014), inflammation may play a role in the subsequent susceptibility to the development of diseases seen in individuals with low birthweight (Black et al., 2004; Mortensen, 2001). There is no clear direction of causality as children with low birth weight have more respiratory infections compared to a control population (Chan et al, 1989), while it is recognized that CRP boosts the innate immune response to bacteria (Ng et al., 2007), with particular activity against *Streptococcus pneumoniae* (Thomas-Rudolph et al., 2007). Further longitudinal studies of the association between birthweight and diseases will be required to clarify these issues, adjusting for serum hsCRP levels in childhood.

TABLE 2 Association between anthropometric measures and systemic inflammation (log hsCRP) at 3 years

Weight measure	Univariate analysis	Model adjusting for municipality	Model adjusting for sex	Model adjusting for municipality and sex
Birthweight (kg)	-0.70 (-1.34 to -0.06)	-0.78 (-1.45 to -0.10)	-0.58 (-1.29 to +0.13)	-0.65 (-1.38 to +0.08)
Weight at 3 years (kg)	-0.05 (-0.22 to +0.13)			—
Change in weight in first 3 years (kg)	-0.02 (-0.22 to +0.19)			—

Beta-coefficient = natural log CRP (mg L^{-1}) per kg increase in birthweight.

In summary, we have identified that in a population of children aged 3 years, there is an inverse association between birthweight and serum hsCRP levels. These data provide one potential explanation for how low birthweight is associated with changes in risk of disease and mortality in later life. Further follow up of this cohort with the particular addition of cardiovascular outcome measures will permit increased understanding of the biological processes that drive these conditions.

ACKNOWLEDGMENTS

This work was supported by the Wellcome Trust (090375); Nottingham University Hospital Charitable Trust; the Nottingham Respiratory Biomedical Research Unit and Instituto Nacional de Higiene, Epidemiología y Microbiología, Havana, Cuba. We would like to thank all of the participants and their families for making this study possible. HINASIC study group (Historia Natural de la Sibilancia en Cuba/National History of Wheezing in Cuba) consists of the following individuals:

National Institute of Hygiene, Epidemiology and Microbiology

Silvia J Venero-Fernández, Ramón Suárez-Medina, Hermes Fundora-Hernández, Lenina Menocal-Heredia, Yuria Isabel Carballo-Sánchez, Félix Manuel Rosado-García, Reina Amelia Quintana, Lourdes Batista Gutiérrez. Patricia Varona-Pérez, María del Carmen Hinojosa.

Hospital Universitario Pediátrico Docente Centro Habana

Regla N. Rivero, Javier Muñoz-Pérez, Caridad González-Morfa.

Municipio de Arroyo Naranjo

Esperanza de la C. Mora-Faife, Damaris Zaldívar-Ricardo, María Teresa Méndez-Ratger, Amed Fernández-Casamayor, Gisela Álvarez-Valdez, Anadelis Alfonso-Hernández, Rob-

erto Hidalgo-Mederos, Nereida Calderin-Martínez, Jorge Antonio Febles-del Toro, Danay Silva, Violeta Suarez-Angelo, Noelvis Zayas-Mompie, Grisel M. Esquivel-Barrios, Zoe de los Angeles Figueroa-Barreto, Olga Lidia Negrin-Molina, Odalis Kessell- Díaz, Mariela de la Caridad Hernández-González, Dulcima Casanave-Guarnaluce, Gretel Comas-Fonseca, Vilma Álvarez-Valdez, María Engracia-Báez Rodríguez, Felicia Sánchez-Cardentey, Nieves Sardinias-Báez, Roberto Esteban Márquez-Solís, Marlene Flores-Carballosa, Nagaby Gómez- Baro.

Municipio de La Lisa

Gladys García-García, María de Lourdes Ortiz-Hernández, María Antonia Betancourt-López, Marlén Batista-Cedeño, Iris Alfonso-Castellanos, Leticia Gómez-García, Ernesto Rafael Gutiérrez-Mendoza, María Luisa Loynaz-González, Nibenía Rodríguez-Trujillo, Yanet Pozo-Herrera, Víctor Manuel Montejo-Guerra, Julia Urbina-Reynaldo, Valentina Gómez-Suliman, Caridad Alicia Rodríguez-Aragón.

Municipio de Cerro

Ileana del Valle-Infante, Claudia Matos-Ramos, Martha Betancourt-Orue, Oscar Alba-Monteagudo, Yuderkis Ferrer-Ceruto, Aída Damas-Martínez, Mercedes Peñalver-Pérez

Municipio de Habana del Este

Liem Gómez-Marrero, Sarahí Castillo-Martínez, Amor de los Angeles Castaño-Vega, Norberto Torriente-Barzaga, Ileana Ávila-Rodríguez, Magalys Navarro-Ruiz, Kirenia Díaz-Hernández, Iluska De La Torre Suarez, Gilberto Roque-Pereira, Yamilet Corona-Carnero, Idania Gonzalaz-Fernandez, Fidelia Romeu-Ravelo, Regla Hernandez-Ponce, Teresa Serrano-González, Dulce Romeo-Cepero, Caridad Gonzalez Leiva, Teresa De Jesus Cobas Espino, Nuris-Fajardo, Midiala Perez-Arcia, Sarahy Diaz-Araujo, Yanet Medina- Lescay, Sandra Collazo-Rodríguez, Julia Amparo Griñán-Ramos, Teresa Serrano-Gonzalez, Beatriz Lazo-Vazquez, Tania Pupo-Portal, Nidia Leyva-Porra, Odalys Pacheco-Mesa, Martha Rizo-Ramos, Yaneysi Vallafuerte-

Perez, Aliniuska De La Paz-Arias, Maite B Garcia-Sotolongo, Yusimí Calzado-Herrera, Martha Nidia Rizo-Ramos, Guillermo Verdecia, Mayté B García-Sotolongo, Juana F Abreu-Quijano, Fidelia Romeo-Ravelo.

Thanks also to all Municipality Directors and the laboratory workers who have also supported the study.

AUTHOR CONTRIBUTIONS

The 8 Cuban authors (SV, HF, LB, RS, EM, GG, IV, LG) came up with the original concept of the study and the study design. AF and JB helped with the study design and obtaining funding. The data were collected by the 8 Cuban authors (SV, HF, LB, RS, EM, GG, IV, LG) and analyzed by RS and AF. All authors contributed to the final drafting and approval of the manuscript.

REFERENCES

- Belson, M., Kingsley, B., & Holmes, A. (2007). Risk factors for acute leukemia in children: A review. *Environmental Health Perspectives*, *115*, 138–145.
- Bhuiyan, A., Srinivasan, S., Chen, W., Azevedo, M., & Berenson, G. (2011). Influence of low birth weight on C-reactive protein in asymptomatic younger adults: The Bogalusa heart study. *BMC Research Notes*, *4*, 71.
- Bindea, G., Mlecnik, B., Fridman, W.-H., Pages, F., & Galon, J. (2010). Natural immunity to cancer in humans. *Current Opinion on Immunology*, *22*, 215–222.
- Black, S., Kushner, I., & Samols, D. (2004). C-reactive protein. *Journal of Biological Chemistry*, *279*, 48487–48490.
- Chan, K., Elliman, A., Bryan, E., & Silverman, M. (1989). Respiratory symptoms in children of low birth weight. *Archives of Diseases in Children*, *64*, 1294–1304.
- Chow, M., Moller, A., & Smyth, M. (2011). Inflammation and immune surveillance in cancer. *Seminars in Cancer Biology*, *22*, 23–32.
- Cook, D., Mendall, M., Whincup, P., Carey, I., Ballam, L., Morris, J., ... Strachan, D. (2000). C-reactive protein in children: Relationship to adiposity and other cardiovascular risk factors. *Atherosclerosis*, *149*, 139–150.
- Cooper, R., Kennelly, J., & Ordunez-Garcia, P. (2006). Health in Cuba. *International Journal of Epidemiology*, *35*, 817–824.
- Danesh, J., Whincup, P., Walker, M., Lennon, L., Thomson, A., Appleby, P., ... Pepys, M. (2000). Low grade inflammation and coronary heart disease: Prospective study and updated meta-analyses. *British Medical Journal*, *321*, 199–204.
- Du Clos, T., & Mold, C. (2004). C-reactive protein. An activator of innate immunity and a modulator of adaptive immunity. *Immunological Research*, *30*, 261–277.
- Fogarty, A., Glancy, C., Jones, S., Lewis, S., McKeever, T., & Britton, J. (2008). A prospective study of weight change and systemic inflammation over 9 years. *American Journal of Clinical Nutrition*, *87*, 30–35.
- Fundora-Hernández, H., Suarez-Medina, R., Venero-Fernandez, S., Mora-Faife, E., García-García, G., del Valle-Infante, I., ... Britton, J. (2014). What are the main environmental exposures associated with elevated IgE in Cuban infants? A population-based study. *Tropical Medicine and International Health*, *19*, 545–554.
- Gillum, R. (2003). Association of serum C-reactive protein and indices of body fat distribution and overweight in Mexican American children. *Journal of National Medical Association*, *95*, 545–552.
- Gluckman, P., Hanson, M., Cooper, C., & Thornburg, K. (2008). Effect of in utero and early-life conditions on adult health and disease. *New England Journal of Medicine*, *359*, 61–73.
- Hjalgrim, L., Rostgaard, K., Hjalgrim, H., Westergaard, T., Thomassen, H., Forestier, E., ... Schmiegelow, K. (2004). Birth weight and risk of childhood leukemia in Denmark, Sweden, Norway and Iceland. *Journal of National Cancer Institute*, *96*, 1549–1556.
- Huxley, R., Owen, C., Whincup, P., Cook, D., Rich-Edwards, J., Davey Smith, G., & Collins, R. (2007). Is birth weight a risk factor for ischemic heart disease in later life? *American Journal of Clinical Nutrition*, *85*, 1244–1250.
- McDade, T., Metzger, M., Chyu, L., Duncan, G., Garfield, C., & Adam, E. (2014). Long-term effects of birth weight and breastfeeding duration on inflammation in early adulthood. *Proceedings of Royal Society London B*, *281*, 20133116.
- McDade, T., Rutherford, J., Adair, L., & Kuzawa, C. (2010). Early origins of inflammation: Microbial exposures in infancy predict lower levels of C-reactive protein in adulthood. *Proceedings of Royal Society London B*, *277*, 1129–1137.
- Mortensen, R. (2001). C-reactive protein, inflammation and innate immunity. *Immunological Research*, *24*, 163–176.
- Mu, M., Wang, S.-F., Sheng, J., Zhao, Y., Li, H.-Z., Hu, C.-L., & Tao, F.-B. (2012). Birth weight and subsequent blood pressure: A meta-analysis. *Archives of Cardiovascular Disease*, *105*, 99–113.
- Ng, P., Saux, A., Lee, C., Tan, N., Lu, J., Thiel, S., ... Ding, J. (2007). C-reactive protein collaborates with plasma lectins to boost immune response against bacteria. *Embo Journal*, *26*, 3431–3440.
- Ostrand-Rosenberg, S. (2008). Immune surveillance: A balance between protumor and antitumor immunity. *Current Opinion in Genetics and Development*, *18*, 11–18.
- Paltiel, O., Harlap, S., Deutsch, L., Knaanie, A., Massalha, S., Tiram, E., ... Friedlander, Y. (2004). Birth weight and other risk factors for acute leukemia in the Jerusalem Perinatal Study Cohort. *Cancer Epidemiology, Biomarkers, Prevention*, *13*, 1057–1064.
- Ridker, P., Buring, J., Shih, J., Matias, M., & Hennekens, C. (1998). Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation*, *98*, 731–733.

- Ridker, P., & Cook, N. (2004). Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham risk scores. *Circulation*, *109*, 1955–1959.
- Ridker, P., Hennekens, C., Buring, J., & Rifai, N. (2000). C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *New England Journal of Medicine*, *342*, 836–843.
- Risnes, K., Vatten, L., Baker, J., Jameson, K., Sovio, U., Kajantie, E., . . . Painter, R., et al. (2011). Birthweight and mortality in adulthood: A systematic review and meta-analysis. *International Journal of Epidemiology*, *40*, 647–661.
- Sattar, N., McConnachie, A., O'reilly, D., Upton, M., Greer, I., Davey Smith, G., & Watt, G. (2004). Inverse association between birth weight and C-reactive protein concentrations in the MIDSPAN family study. *Arteriosclerosis, Thrombosis and Vascular Biology*, *24*, 583–587.
- Simons, J., Loeffler, J., Al-Shawi, R., Ellmerich, S., Hutchinson, W., Tennent, G., . . . Read, K. (2014). C-reactive protein is essential for innate resistance to pneumococcal infection. *Immunology*. doi: 10.1111/imm.12266.
- Spinreact high sensitivity CRP assay. 2016. Available at: [http://www.spinreact.com/files/Inserts/SERIE_SPINTECH_\(TKB\)/Turbilatelx/TKCRP_4-1_CAL_liof_2012pdf](http://www.spinreact.com/files/Inserts/SERIE_SPINTECH_(TKB)/Turbilatelx/TKCRP_4-1_CAL_liof_2012pdf) (accessed 4/7/2016)
- Stata Corp. 2016. Available at: <http://www.stata.com/manuals14/u.pdf> (accessed 4/7/2016).
- Suarez-Medina, R., Venero-Fernandez, S., Mora-Faife, E., García-García, G., del Valle-Infante, I., Gómez-Marrero, L., . . . Fundora-Hernández, H. (2014). Risk factors for eczema in infants born in Cuba. *BMC Dermatology*, *14*, 6.
- Thomas-Rudolph, D., Du Clos, T., Snapper, C., & Mold, C. (2007). C-Reactive protein enhances immunity to *Streptococcus pneumoniae* by targetting uptake to FC-gammaR on dendritic cells. *Journal of Immunology*, *178*, 7283–7291.
- Tzoulaki, I., Marjo-Riitta, J., Hartikainen, A.-L., Leinonen, M., Pouta, A., Paldanius, M., . . . Saikku, P. (2008). Size at birth, weight gain over the life course, and low-grade inflammation in young adulthood: Northern Finland 1966 birth cohort study. *European Heart Journal*, *29*, 1049–1056.
- Venero-Fernandez, S., Suarez Medina, R., Mora Faife, E., García García, G., del Valle Infante, I., Gómez Marrero, L., . . . Fundora Hernández, H., (2013). Risk factors for wheezing in infants born in Cuba. *Quarterly Journal Medicine*, *106*, 1023–1029.
- Zacho, J., Tybjaerg-Hansen, A., & Nordestgaard, B. (2010). C-reactive protein and all-cause mortality—The Copenhagen city heart study. *European Heart Journal*, *31*, 1624–1632.