UNIVERSITY OF CALIFORNIA, SAN DIEGO
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Interconnectedness of Micronutrient Deficiency and Obesity in Children: Impact of Dual Burden of Nutritional Disorders and Two-hit Insult

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

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by

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2016

DEDICATION

"Dedicated to the Author of my life's story, who penned in blood ink the happiest of all endings"

– Patricia Goodson

This dissertation represents the culmination of years of study and commitment to the field of global nutrition and child development and is dedicated to my family: Pablo Won-Young Kang, Christine Wanjoo Kang Sim, and Ceon Kang. Without their support and encouragements, I will not be here where I am today. It is also devoted to my faith community in San Diego State University: Paul Minbo Shim, Ashley KeunHye Park, Zach Gallardo, who selflessly supported me throughout this journey. Lastly, this dissertation is dedicated to many faculty members and Chile research team who entrusted me to study Global Health.

TABLE OF CONTENTS

SIGNATURE PAGE ..... **iii**
DEDICATION ..... **iv**
TABLE OF CONTENTS ..... **v**
LIST OF FIGURES AND TABLES ..... **viii**
ACKNOWLEDGEMENTS ..... **ix**
VITA ..... **x**
ABSTRACT OF THE DISSERTATION ..... **xiii**
CHAPTER 1: INTRODUCTION **1**
OVERVIEW 1
BACKGROUND 4
The global burden of iron deficiency and obesity 4
Adverse brain-behavior consequences of iron deficiency and obesity 5
Study setting 7
Theoretical and statistical interaction concepts 9
Aims and hypotheses 13
Global health implications 14
REFERENCES 17
CHAPTER 2: THE IMPACT OF ECONOMIC GROWTH AND NUTRITIONAL CHANGES ON THE BURDEN OF UNDERNUTRITION AND OBESITY IN CHILDREN IN BRAZIL, CHILE, AND MEXICO **22**
ABSTRACT 22
INTRODUCTION 23
Aim of this review 24
METHODS 25
Review of governmental nutrition policies 26
Conceptual framework 26
Measures 26
Analysis 29
Data sources 29
REVIEW OF GOVERNMENTAL NUTRITIONAL POLICY 30
Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Brazil 30
Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Chile 31

Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Mexico 32
Synthesis, successful government nutritional policy on reducing the prevalence of calorie-based undernutrition 33
EMPIRICAL EVIDENCE OF IMPACT OF ECONOMIC GROWTH AND NUTRITIONAL CHANGES 33
Trends of gross national income: comparison among Brazil, Chile, and Mexico 33
Synthesis, impact of economic growth on child nutritional outcomes 34
Trends of food availability and the quality of diets on child nutritional outcomes 35
Synthesis, impact of nutritional changes on child nutritional outcomes: comparison among Brazil, Chile, and Mexico 36
Evidence of correlation between increased sedentary behavior and child obesity: comparison among Brazil, Chile, and Mexico 37
DISCUSSION: DUAL BURDEN CHALLENGES 37
CONCLUSIONS 40
ACKNOWLEDGEMENTS 42
REFERENCES 47
CHAPTER 3: THE IMPACT OF INFANT IRON DEFICIENCY AND ADOLESCENT OVERWEIGHT STATUS ON NEUROCOGNITIVE PERFORMANCE DURING ADOLESCENCE: A TEST OF TWO-HIT NUTRITIONAL INSULT HYPOTHESIS 51
ABSTRACT 51
INTRODUCTION 53
METHODS 54
Study design and participants 54
Measures 56
RESULTS 58
DISCUSSION 59
Public health implication 61
Limitations and future studies 62
Conclusion 63
ACKNOWLEDGEMENTS 64
REFERENCES 68
CHAPTER 4: THE ADDITIVE IMPACT OF INFANT IRON DEFICIENCY AND ADOLESCENT OVERWEIGHT STATUS FOR YOUTHS' EXTERNALIZING PROBLEM BEHAVIOR: TESTING A TWO-HIT NUTRITIONAL INSULT HYPOTHESIS 71
ABSTRACT 71
INTRODUCTION 73

METHODS....74
Study site....74
Design and sampling....75
Measures....75
Statistical analysis....77
RESULTS....78
DISCUSSION....80
Limitation....83
Conclusion....83
ACKNOWLEDGEMENTS....84
REFERENCES....88
CHAPTER 5: DISCUSSION....92
THE DUAL BURDEN OF NUTRITIONAL DISORDERS....92
The need for integrated interventions....92
THE TWO-HIT INSULT AND BRAIN-BEHAVIORAL MANIFESTATION....94
Causal interaction between iron deficiency and weight status?....95
STRENGTHS AND LIMITATIONS....97
Generalizability....97
Statistical power and measurement....99
RECOMMENDATIONS AND FUTURE RESEARCH NEEDS....99
CONCLUSIONS....100
REFERENCES....102

LIST OF FIGURES AND TABLES

Figure 1.1. Conceptual framework linking economic development, food supply, behavioral pattern, and nutritional status 16

Figure 2.1. Conceptual framework linking economic development, food supply, behavioral pattern, and nutritional status 42

Figure 2.2. Trend lines of calorie-based nutrition and micronutrient indicators with gross national income from 1990 to 2010 43

Figure 2.3. Trend lines of quality and supply of food with per capita food availability from 1990 to 2010 44

Figure 2.4. Changes of market penetration of TV service subscription in Brazil, Chile, and Mexico from 2005 to 2010 45

Figure 3.2. Covariate-adjusted means of reaction time (msec) and accuracy (%) by nutritional insult status 63

Table 3.1. Characteristics of participants 62

Table 3.2. Regression coefficients and attributable proportion 64

Table 4.1. Descriptive characteristic 81

Table 4.2. Impact on index of multiplicativity: odds of exhibiting externalizing behavior disorder above clinical cutoffs 82

Table 4.3. Impact on indices of additivity: betas from linear binomial regression, relative excess risk due to interaction, attributable proportion, and synergy index 83

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2. Miguel Pinedo, D. Eastern Kang Sim, Rebeca Espinoza, Maria Zúñiga (2015). An exploratory study of internal migration and substance use among an indigenous community in Southern Mexico. *Family and Community Health.*
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ABSTRACT OF THE DISSERTATION

Interconnectedness of Micronutrient Deficiency and Obesity in Children:

Impact of Dual Burden of Nutritional Disorders and Two-hit Insult

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Background: The coexistence of micronutrient deficiencies and obesity and their adverse effect on children's development is understudied.

Aims: The aims of this dissertation were to: 1) describe the link between economic changes and child nutritional outcomes by linking indicators related to immediate and underlying determinants; 2) assess neurocognitive outcomes of response inhibition and accuracy to adolescents exposed to 'iron deficiency/iron deficiency anemia (ID/IDA) in infancy', 'overweight/obesity (OW/OB) in adolescence', or 'both' compared to those without these conditions; and 3) assess the adverse outcome of youth externalizing behavior problem exposed to 'ID/IDA in infancy', 'OW/OB in adolescence', or 'both' compared to those without these conditions.

Methods: Study 1 focuses on the economic growth and nutrition profiles of Brazil, Chile, and Mexico from 1990 to 2010. Estimates for all indicators were retrieved and reconstructed from data sources including the Ministry of Health of each country, the Organization of Economic, and Co-operation and Development and Food Agriculture Organization of the United Nations. Study 2 and 3 uses data from a longitudinal cohort study of Chilean infants who participated in a randomized controlled trial of iron to prevent iron deficiency anemia were used. The Stroop computerized task was used to assess individual's reaction times and accuracy. The Achenbach's Youth Self Report was used to assess clinically meaningful externalizing behavior problem.

Results: Study 1, presents evidence indicating that economic growth affects child nutritional outcomes through several pathways. Study 2 found that the

combination of poorer brain-circuit development during infancy due to ID/IDA and the inflammation of fat due to adolescent OW/OB may have additive effects on reaction times. Study 3 found that adolescents who experienced a two-hit insult of ID/IDA and OW/OB had a positive deviation from additivity (RERI=1.4; S=2.9; AP=40%) and multiplicativity (OR=1.7; 95% CI: 1.1, 2.7) on youth externalizing behavior problem.

Conclusion: The dual burden of nutritional disorders among children are closely linked to their economic growth and nutritional transition. The two-hit insult concept proved useful in understanding the additive and multiplicative effects of two independent nutritional insults and warrants further application.

CHAPTER 1: INTRODUCTION

OVERVIEW

Latin America experienced remarkable rates of economic growth between 1990 and 2010.[1] Despite this growth, however, not all members of these societies benefited sufficiently from the region's economic growth during this period as, in 2011, more than 177 million Latin Americans continued to live in poverty.[2,3] Among poor and vulnerable groups, children were affected most often by nutritional insults and poor health outcomes.[4,5] Economic growth had both intended and unintended consequences that impacted child health.[6] Intended outcomes included improved access to sufficient amounts of food, which in turn lowered the prevalence of children with calorie-based undernutrition and a significant decline in infant mortality due to reduction in infectious and respiratory diseases.[7-10] However, studies also suggest that the economic growth produced unintended negative health consequences for children by shifting countries' nutritional profiles from insufficient to an excessive intake of calorie and proteins.[6,8,9,11] The problem has been exacerbated by increased exposure to obesogenic environments, including an increased prevalence of physically inactive populations.[12-14] Moreover, despite improvements in markers of overall calorie-based undernutrition, the prevalence of children with micronutrient deficiencies remains widespread, indicating a continued lack of comprehensive nutrients to maintain robust health.[15,16] As a consequence, Latin American countries and many transitioning countries are now faced with a 'dual burden of

nutritional disorders' (DBND), a new concept introduced to describe the paradox of the coexistence of undernutrition and overweight/ obesity in the same population.[17-20] This phenomenon, which is currently at epidemic levels, is a cause for concern as stunted children are more likely to be developmentally programmed for obesity in later years.[21,22]

To date, no studies have reviewed the impact of economic changes on child nutritional outcomes in Latin American settings, and the lack of understanding on this topic represents a significant gap in the literature. **Chapter 2** of this dissertation presents the intended and unintended consequences of economic growth on child health in three Latin American countries by describing policies and strategies undertaken to reduce the prevalence of calorie-based undernutrition and examines the impact of economic growth and changes in food quality and availability on child nutritional outcomes.

Additionally, this dissertation will delineate the potential adverse outcomes for *individuals* exposed to both infant iron deficiency and adolescent overweight status. Given that infants comprise a high proportion of those affected by iron deficiency and iron deficiency anemia, and the fact that the prevalence of adolescent obesity is rapidly increasing, the current lack of research on this topic represents a significant gap in the literature. That is, it is plausible that having iron deficiency status in infancy and overweight status in adolescence may put an individual at higher risk of decreased neurocognitive functioning than individuals experiencing either condition alone.[23-28] Moreover, as the interaction between an individual and the environment must be channeled through the brain,

it is likely that slower processing speeds caused by nutritional insults can be translated into behavioral manifestations that are maladaptive. With the brain as the primary determinant of behavior, damage caused by iron deficiency in infancy and the negative health effects of overweight or obesity during adolescence may put individuals with exposure to both conditions at greater risk for behavioral difficulties than those with one or neither condition.

To the best of our knowledge, there are no previous studies that describe adverse brain-behavior outcomes in *individuals* with joint exposures to iron deficiency in infancy and overweight/obesity in adolescence. To address this gap in the literature, **Chapter 3** of this dissertation assesses the neurocognitive outcomes of response inhibition in adolescents exposed to iron deficiency/iron deficiency anemia (ID/IDA) in infancy, overweight/obesity (OW/OB) in adolescence, or both conditions compared to those without these exposures. **Chapter 4** assesses clinically meaningful cutoff for referral of externalizing problem behavior among adolescents exposed to ID/IDA in infancy, OW/OB in adolescence, or both exposures compared to those without these conditions. In both chapters, we hypothesize that adolescents with joint exposures will demonstrate greater adverse effects on diagnostic assessments of neurocognitive functioning and assessments of externalizing behavior problems compared to those with one exposure or no exposures.

BACKGROUND

The global burden of iron deficiency and obesity

According to the World Health Organization, iron deficiency and obesity are the most common widespread nutritional disorders in the world.[10,29] The 2010 report on the Global Burden of Disease ranked iron deficiency as one of the top five risk factors contributing to Disability-Adjusted Life Years in children between 1 and 15 years of age in all regions of Latin America.[30,31] With increased caloric intake and globalization of the food supply, many children who were at risk from iron deficiency in their early years, were also at risk for obesity later in life.[8,9,19,32] Indeed, obesity rates have increased more rapidly than the decline in underweight children throughout the world. Studies suggest that the main factor associated with the DBND is the nutrition transition, which describes the way economic development impacts and changes a population's dietary behavior as well as their nutritional profile.[7,9,19,32-34] This shift often coincides with a demographic migration from rural to urban areas, economic development, urbanization, and some biological factors. During these economic and nutritional transitions, undernourishment and infectious disease tend to disappear and are gradually replaced with overweight/obesity and chronic diseases; however, micronutrient deficiencies continue to be widespread, making developing countries an ideal setting for the coexistence of micronutrient deficiencies and obesity. The Latin America region had successfully reduced the prevalence of undernourished children, but most experts believe that many more people that suffer from vitamin and mineral deficiencies and obesity than the estimated 842

million people suffer from undernourishment.[2] An accurate estimate of the incidence of combined nutritional disorders has not yet been determined because hidden hunger, which is caused by a chronic lack of vitamins and minerals, has no visible warning signs. Horton and Ross examined the impact of a variety of functional consequences of iron deficiency along with their economic implications using data from ten developing countries. Accounting for both physical and cognitive impairment in children and adults, the mean losses amount to 4.05% of Gross Domestic Product.[35] Likewise, the negative economic impact of obesity in the United States is substantial, and simple addition of the key effects associated with obesity have a total annual economic cost of $215 billion USD.[36] Clearly, countries undergoing economic and nutritional transitions will be entangled in the economic and health consequences of DBND. To our knowledge, no studies to date have reviewed the impact of economic growth and nutritional changes on child nutritional outcomes in Latin American settings. The review in Chapter 2 seeks to address this gap by examining the impact of economic growth and changes in food quality and availability on child nutritional outcomes along with a description of the policies and strategies undertaken by transitioning countries to reduce the prevalence of calorie-based undernutrition.

Adverse brain-behavior consequences of iron deficiency and obesity

Over the past several decades, there has been an overwhelming increase in the amount of research dedicated to better understanding how nutritional status influences cognition and behavior.[37-39] Considering the impact that

nutritional disorders have on brain-behavior manifestations from infancy through adulthood, studies have confirmed the importance of several individual nutrients and diets in brain development and functioning in children and adolescents.

One of the most essential nutrients during early brain development is iron, and its deficiency is the most prevalent micronutrient deficiency in both the developing and developed parts of the world. Much evidence shows that brain development is compromised when iron deficiency is moderate to severe, and it has been shown to cause neurocognitive dysfunction both during deficiency and after repletion.[40-42]

If early infancy is a critical time period for brain development (e.g. brain-circuit development), adolescence is a sensitive time period for brain maturation and performance. Studies suggest that adolescent overweight or obesity is correlated with poorer executive functioning and obese adolescents' body mass index is inversely related to performance on the Stroop Color-Word Interference Test.

A significant gap in the literature remains as the majority of the studies between nutrition and cognitive development investigate on one point in time or focus on individual nutrient or diet, and do not take into account that nutrients often act synergistically in some contexts. As the variation in intake (insufficient or excessive) of macro- and micronutrients impact cognitive development and function at different life stages, the additive effect of the ID/IDA in infancy and OW/OB in adolescence may have independent and more serious adverse effects on brain-behavioral outcomes then experiencing either condition alone. Chapters

3 and 4 explore a ‘two-hit’ insult hypothesis defined by individuals who were exposed to ID/IDA in infancy and OW/OB in adolescence, which have been hypothesized to have greater adverse effects on neurocognitive functioning and externalizing behavior problems in later years.

Study setting

To illustrate how high rates of economic growth have impacted Latin American populations’ nutritional profiles, **Chapter 2** focuses on the economic growth and nutrition profiles of Brazil, Chile, and Mexico. From 1990 to 2010, these three countries experienced significant economic growth and have concomitantly developed high rates of childhood obesity. All relevant data are available through their memberships in the Organization of Economic Co-operation and Development and the Food Agriculture Organization of the United Nations.

Chapters 3 and 4 present a secondary data analysis using a longitudinal study from Santiago (Santiago Longitudinal Study), Chile.[43] Participants were recruited from low-to middle-income communities in Santiago from 1991 to 1996. From the time of inclusion in the study, the children were evaluated every 6 weeks to 18 months and their growth, health, and development were routinely documented at 5yo, 10yo, and adolescence. Data from infancy and adolescence were used for this analysis. Informed consent was provided by all participating families and ascent to participants at the time of the adolescent wave. The Institutional Review Boards of the relevant universities approved the study.

The setting of the proposed research in Chile is close to ideal for studying the long-term effects of iron deficiency anemia in infancy because the original iron deficiency anemia prevention trial was conducted at a time when nutritional iron deficiency was common, while other risk factors for anemia were essentially absent. Furthermore, while Chile eradicated moderate to severe calorie-based undernutrition in children by 1990,[44] the increased intake of high-caloric food and exposure to obesogenic environments caused the burden of obesity to increase exponentially.[45] These principal characteristics of a nutrition transition period make the Santiago Longitudinal Study a unique opportunity to study adverse effects of the two-hit insult hypothesis on brain-behavior manifestations.

THEORETICAL AND CONCEPTUAL FRAMEWORKS

Adaptation of UNICEF's conceptual framework of malnutrition

The study reported in **Chapter 2** was conceptualized based on the United Nations Children's Emergency Fund (UNICEF)'s framework of malnutrition, which presents a broad spectrum of multi-causal and multi-factorial determinants.[46] According to this framework (Fig 1), the determinants are divided into four categories: nutritional outcomes and immediate, underlying, and basic determinants. For nutritional outcomes, we studied undernutrition, calorie-based undernutrition, micronutrient deficiencies, and overweight/obesity in children under five years of age. Immediate determinants refer to individual factors and behavior patterns, whereas underlying determinants relate to availability and access to food and services at the community level. We chose indicators of the

‘quality of diet’ and ‘food availability’ from the Food and Agriculture Organization of the United States. We defined the quality of diet as the per capita supply of fruits, excluding wine; vegetables; fats derived from animals; and meat. For the indicator of ‘food availability,’ we utilized the concept of ‘average dietary supply adequacy,’ which expresses the dietary energy supply as a percentage of the average dietary energy requirement in each country.[47] In the case of childhood overweight and obesity, indicators of food availability only tell part of the story. We used publicly available data on trends of market penetration of a pay TV service subscription from the Latin American Multichannel Advertising Counsel as a proxy for increased trends of sedentary behavior and obesity. Lastly, basic determinants refer to the way in which a society is organized in terms of resources, materials, and wealth. We chose Gross National Income per capita to describe how per capita income changed during specific time periods.

Theoretical and statistical interaction concepts

Studies reported in **Chapters 3 and 4** were based on the concepts of joint effect or interaction.[48-50] In brief, there are two different concepts of interaction that should be distinguished: the theoretical concept of causal interaction and the concept of statistical interaction. The notion of causal interaction is when two risk factors act together to create an outcome, and is explicitly defined as a deviation from additivity of the risk difference scale of the two risk factors under study. This means that the joint effect of two exposures is more or less than the sum of their separate effects. Causal interaction happens all the time in biology, but it is

important to note that an observed joint effect may not imply anything about the underlying biological mechanisms.

Statistical interaction, on the other hand, refers to the inclusion of a product term of the two risk factors under studying a statistical model. Depending on the model that is used, it can be evaluated on both an additive (absolute risk) and multiplicative (relative risk) scale. In other words, statistical interaction is dependent upon the underlying scale: if an additive model is employed, a statistically significant product term indicates deviation form additivity, whereas a statistically significant product term in a multiplicative model indicates deviation from multiplicativity. Linear and logistic regression analyses are important statistical tools for assessing relationships between exposure and outcome and for controlling covariates. Linear regression analysis demands that the outcome variable is continuous, whereas logistic regression analysis demands that the outcome variable is dichotomous. To summarize the differences between linear and logistic regression techniques in assessing joint effect, the following equations show that the underlying scales of these models are different:

Eq. 1.1 The regression equation of the linear regression model including product term:

$$E(y)=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

where E (y) is the estimated value of the outcome variable Y, β_0 is the intercept or background risk, β_1 and β_2 are the regression coefficients of the risk factors X_1

and X_2. By including the product term ($X_1 * X_2$) the interaction effect is estimated through estimation of the regression coefficient β_3. When the regression coefficient β_3 tests significant, that would mean the effect on outcome Y is β_3 much different when $X_2 = 1$ compared to when $X_2 = 0$. Since linear regression models are additive models, a statistically significant regression coefficient of β_3 indicates a deviation of additivity ($\beta_3 > (\beta_1 + \beta_2)$), implying the presence of interaction on an additivity scale, or parameters X_1 and X_2 are said to have 'additive' effects on the outcome.

In contrast, logistic models are by definition multiplicative models. The equation below shows the logistic regression model including an interaction term:

Eq. 1.2 The regression equation of the logistic regression model including product term:

$$\ln [p/(1-p)] = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$$

or

$$[p/(1-p)] = e^{(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2)}$$

or

$$[p/(1-p)] = e^{\beta_0} * e^{\beta_1 X_1} * e^{\beta_2 X_2} * e^{\beta_3 X_1 X_2}$$

where 'p' is the proportion of individuals with the outcome and [p/1-p] is the odds of the outcome. Using the logistic regression model, a statistically significant product term between two risk factors implies departure from multiplicativity, rather than from additivity. The product term β_3 can still be said to be 'additive'

only on the logarithmic scale. This would require back-transformation of logarithmic parameters to the probability scale. This process can be quite tricky especially in the presence of covariates. This is because homogeneity of covariate effects on and odds ratio scale is not the same as homogeneity on a risk difference scale.[51]

Thus, depending on the model (linear or logistic) that is used, the interaction effect is tested on an additive (risk difference) or a multiplicative (relative risk) scale. To address this issue, several strategies were developed for testing additive interactions when the outcome of interest is dichotomy: 1) Directly fit $E(y)=\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1 X_2$ using *linear binomial* regression. Although use of *linear binomial* regression is not widely used by epidemiologists, it is standard practice among economist and is frequently referred to as the linear probability model.[52] Any potential bias is lessened as the relative proportion of predicted probabilities lying inside the unit interval increases.[53] Confidence intervals and standard errors can easily be corrected using profile likelihood confidence intervals and robust standard errors in preference over Wald-type confidence intervals. A considerable advantage of using this first strategy is that it is an additive model by definition. 2) Estimation of indices of additive interaction were developed to evaluate interaction on additive scale using relative measures of effect derived from multiplicative models. Three different measures exist to quantify the amount of interaction on an additive scale [50,54]: a) the relative excess risk due to interaction (RERI), which can be interpreted as the risk that is additional to the risk that is the expected basis of the additional to the risk that is

expected on the basis of the addition of the odds ratios under exposure; b) the attributable proportion due to interaction (AP), which is interpreted as the proportion of disease that is due to interaction among persons with both exposures; c) the synergy index (S), which can be interpreted as the excess risk from exposure to both exposures when there is interaction relative to the risk from exposure without interaction. The effect of statistical interaction of deviation from additivity was explored in **Chapter 3**. Two strategies for statistically testing additivity in bivariate outcome were explored in **Chapter 4.**

Aims and hypotheses

The preceding discussion about the DBND and interaction of deviation form additivity vs. multiplicativity, has immense relevance for the theory of syndemics. At the population level, the term syndemic refers to two or more epidemics interacting synergistically and contributing to excess disease load in a population. At the individual level, the term syndemic refers to the health consequences of the biological interaction that occurs when two or more diseases or health conditions are co-present in multiple individuals within a population. Based on our theoretical and conceptual framework and review of the relevant literature, the organization of the dissertation and the aims and hypotheses are listed below:

Aim 1: To describe the linkage from economic changes to child nutritional outcomes by linking a set of indicators related to immediate and underlying determinants.

Aim 2: To assess the neurocognitive outcomes of response inhibition and accuracy of adolescents exposed to ‘IDA in infancy’, ‘overweight/obesity in adolescence’ or ‘both’ compared to those without the conditions.

Hypothesis: Adolescents exposed to ‘IDA in infancy,’ ‘overweight/obesity in adolescence,’ or ‘both’ will have a) longer reaction times and more errors during diagnostic assessments of neurocognitive functioning and b) lower educational attainment compared to individuals without these conditions.

Aim 3: To assess the adverse outcome of externalizing behaviors in adolescents exposed to ‘IDA in infancy’, ‘overweight/obesity in adolescence’ or ‘both’ compared to those without these conditions.

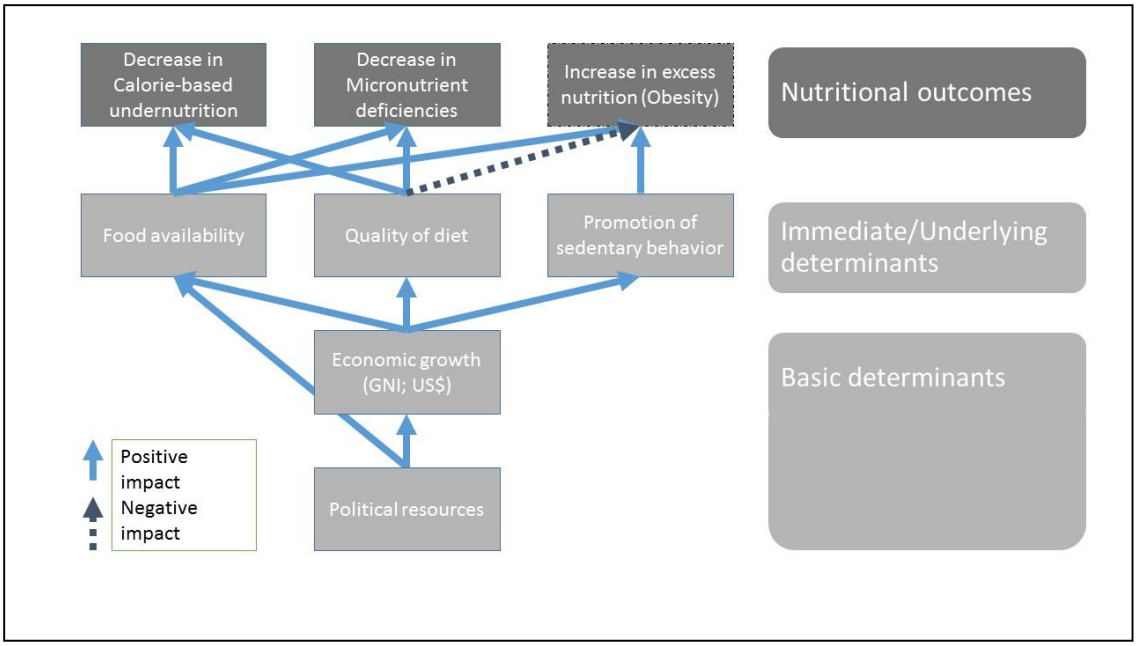
Hypothesis: Adolescents exposed to ‘IDA in infancy,’ ‘overweight/obesity in adolescent,’ or ‘both’ will have an increased risk of externalizing behavior problems compared to those without these conditions.

Global health implications

The review presented in Chapter 2 will be the first to compare population-based child malnutrition in all its forms and provide evidence for the existence of the DBND, whereby both undernutrition and overnutrition coexist in the same population. Results may contribute to a greater understanding of the global health challenges related to the increasing prevalence of chronic disease in low- to middle-income countries. By linking a set of specific indicators, this review

seeks to provide a clearer understanding of the widespread global nutrition epidemic in the context of Latin American children.

Chapters 3 and 4 seek to improve the understanding of the joint exposure of the relationship between iron deficiency status and weight status in order to inform the prioritization of limited resources for integrated nutritional intervention towards vulnerable populations in transition countries.



Adopted from the UNICEF conceptual framework of malnutrition. 'Increase in excess nutrition' has been added to present the case of dual burden of micronutrient deficiencies and obesity.

Figure 1.1. Conceptual framework linking economic development, food supply, behavioral pattern, and nutritional status

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CHAPTER 2: THE IMPACT OF ECONOMIC GROWTH AND NUTRITIONAL CHANGES ON THE BURDEN OF UNDERNUTRITION AND OBESITY IN CHILDREN IN BRAZIL, CHILE, AND MEXICO

ABSTRACT

This review compares country-level economic growth with population-based child nutrition data from Brazil, Chile and Mexico to explore the dual burden of nutritional disorders, whereby both undernutrition and overnutrition (i.e., overweight and obesity) coexist in the same population. This study contributes to an improved understanding of global health challenges associated with economic development including increasing prevalence of nutrition-related chronic disease in low- to middle-income countries. By linking a set of specific indicators, this review seeks to provide a clearer understanding of widespread global nutrition problems among Latin American children in the context of economic transition.

Keywords: Nutrition, transition countries, Brazil, Chile, Mexico, child nutritional outcomes, economic transition, nutrition transition

INTRODUCTION

Latin America has undergone remarkable rates of economic growth between 1990 and 2010. Policies that emphasized social protection, such as poverty reduction and access to care, were key factors in building present-day societies that are more inclusive and promote a minimum standard of living for all, including better physical and mental health. For instance, based on the Economic Commission for Latin America and the Caribbean, the region's total Gross Domestic Product (GDP) increased from 2.7 trillion US dollars in 1990 to 5.1 trillion US dollars in 2010. The GDP per capita also increased from 6,155 US dollars to 8,677 US dollars over 20 years. During this economic transition, access to sufficient food improved which led to decreased child calorie-based malnutrition, reductions in infectious and respiratory diseases and significant decline in infant mortality.[3,4] Despite efforts made by Latin American governments to improve the wellbeing of their citizens, not all population segments have benefited equally from the region's economic growth.[1,2] For example, more than one third of Latin Americans (177 million) continued to live in poverty in 2010.[5] Among poor and vulnerable groups, children have been most impacted by nutritional inequities and poor health.[2,6]

Studies suggest that along with the important successes of decreasing malnutrition and infant mortality, Latin America's economic growth has also produced unintended consequences for children. While caloric intake has increased, energy expenditure has decreased resulting in soaring prevalence of childhood obesity in certain sectors.[7-9] Some factors related to the increased

prevalence of childhood obesity include easy access to inexpensive, low nutritional value and energy-dense foods, greater reliance on cars for transportation and fewer opportunities for exercise. This increase in obesity has taken place at a more rapid rate among children from poor families.[10] In the context of resource-limited families in countries that have undergone economic transitions, it is now common to observe concurrent obesity and calorie-based undernutrition within the same household.[11-13] Moreover, despite declines in markers of overall calorie-based undernutrition such as short stature and underweight, the prevalence of micronutrient deficiencies (e.g., iron, iodine, zinc) in children remains high. Thus, all Latin American countries undergoing recent economic transition are now faced with a 'dual burden' of nutritional problems, a paradox of the coexistence of undernutrition and obesity in the same population.[14-16]

The current study will focus on the economic growth and nutrition profiles of Brazil, Chile, and Mexico. From 1990 to 2010, these three countries experienced significant economic growth and have concomitantly developed high levels of childhood obesity. To the best of our knowledge, there are no Latin American studies assessing population-based child-specific nutritional status related to country-level economic growth, especially by comparing indicators related to determinants of undernutrition and obesity.

Aim of this review

The aims of this review paper are to identify factors that lead us to understand the coexistence of nutritional disorders among children in Brazil,

Chile and Mexico and explore and evaluate strategies for its prevention. We describe policies and strategies undertaken by each country to reduce the prevalence of calorie-based undernutrition. We then examine the impact of economic growth and changes in food quality and availability on child nutritional outcomes. We conclude with key lessons to inform future nutritional policies for countries undergoing similar economic and nutritional transitions. Better-informed health policies can then lead to development of more effective interventions to prevent and reduce the effects of nutritional disparities and burden of disease experienced by children and improve childhood health globally.

METHODS

Numerous factors impact the burden of undernutrition and obesity in children. Fig. 1 provides an overview of the factors that influence the burden of undernutrition and obesity in children. Clearly, the task of designing strategies for preventing ‘dual burden of nutritional disorders’ is complex given the multifactorial nature of the problem. We will organize our review into two categories: 1) review of successful governmental nutritional policies for reducing the burden of a single nutritional disorder, and 2) review of empirical evidence of impact of economic growth and nutritional changes on the burden of multiple nutritional disorders. Unless otherwise noted, the summary of findings for each country is provided in alphabetical order (Brazil, Chile, and Mexico).

Review of governmental nutrition policies

We describe and provide a critical view of national strategies and programs that were enacted in Brazil, Chile, and Mexico from 1990 to 2010 and were designed to reduce the prevalence of undernutrition in each country and conclude the review by addressing the ongoing challenges of concurrent obesity. The information of nutritional program evaluation originates from reports published by government institutions from the respective countries.

Conceptual framework

To demonstrate empirical evidence of linkages between economic growth and nutritional changes on the burden of undernutrition and obesity in children, we adopted and modified UNICEF's conceptual framework of malnutrition, which presents a broad spectrum of multi-causal and multi-factorial determinants.[17] In the conceptual framework (Fig 1), the determinants are divided into four categories: outcomes and immediate, underlying, and basic determinants. Following are definitions and indicators for each determinant:

Measures

Child nutritional outcomes

We studied undernutrition, calorie-based undernutrition and micronutrient deficiencies, and overweight/obesity in children under five years of age. For calorie-based undernutrition, the following variables were used: underweight (inadequate weight-for-age; less than 2 standard deviations under NCHS standard) and stunting (inadequate height-for-age; less than 2 standard deviations under NCHS standard). For micronutrient deficiencies, data showing

the prevalence of vitamin A deficiency in the population and anemia in children under five years old is used to illustrate how the prevalence of micronutrient deficiencies has changed in the selected countries. We defined the prevalence of micronutrient deficiencies in children 'high' and 'widespread' if the prevalence is greater than 10%. Other micronutrients, such as vitamin B12, zinc, and selenium are also critical for comprehensive nutrition, but estimates and data are not readily available in national studies. Data on obesity, body mass index (BMI) ≥ 95th%ile was studied for all 3 countries. Data on prevalence of overweight/obese, BMI ≥ 85th%ile, was available for Brazil and Mexico.

Immediate / underlying determinants

Immediate determinants refer to individual factors and behavior patterns, whereas underlying determinants relate to availability and access to foods and services at the community level. As evidence of food security, we chose indicators of the 'quality of diet' and 'food availability' (average dietary supply adequacy) from the Food and Agriculture Organization of the United Nations (FAO). The 'supply of quality diets' is defined as the per capita supply of fruits, excluding wine; vegetables; fats derived from animals; and meat. All indicators for the 'supply of quality diets' are expressed in kilocalories per capita per day (kcal/capita/day). For the indicator of 'food availability,' we utilized the concept of "average dietary supply adequacy", which expresses the dietary energy supply as a percentage of the average dietary energy requirement in each country. To provide an index of adequacy of the food supply in terms of calories, the FAO provided estimates of each country's total supply of food which is converted into

energy units relative to the amount of calories needed to maintain the population's long-term health.[18] The repeated estimates of per capita consumption of meat, fats derived from animals, fruits, and vegetables were not available.

In the case of childhood overweight and obesity, indicators of food availability only address one aspect of the problem. Obesity is a complex, multifaceted nutritional disorder associated with prolonged individual behavioral programming, influenced by peers, family and environment. While indicators for economic growth and increased food supply may explain, to some degree, the decrease in prevalence of calorie-based undernutrition and persistent problem with micronutrient deficiencies, they do not factor in sedentary lifestyles, which directly increase the prevalence of obesity. Studies show that indicators of sedentary behaviors, especially television (TV) watching, are associated with increased obesity.[19] While country-level indicators of sedentary behavior are scarce, a trend towards increased sedentary behaviors can be inferred from publicly available data. We used publicly available data on trends of market penetration of pay TV service subscription from the Latin American Multichannel Advertising Counsel (LAMAC) as a proxy for increased trends of sedentary behavior and obesity. Studies suggest that families with pay TV subscriptions are also more likely to have automobiles and electronics, which promote overall physical inactivity and sedentary behavior. This method is based on the assumption that as low-income families increase their income, they would seek out appliances such as televisions, and more convenience and time-saving

products such as communication devices, prepared foods, and ready-made products as predicted by the Latin American Consumer 2020 report.[20,21]

Basic determinant

Basic determinants refer to the way in which society is organized in terms of resources, materials, and wealth. We chose Gross National Income per capita (GNI; in US$) to describe how per capita income changed during specific time periods. GNI is a valid measure to compare across countries as it uses the World Bank Atlas method and adjusts for the exchange rate and differences in rates of inflation between countries.

Analysis

For each indicator, we assessed trends between 1990 and 2010 within each country. We then compared these indicators to three nutritional outcomes (calorie-based undernutrition, micronutrient deficiencies, and overnutrition) in order to evaluate empirical evidence for the existence of the dual burden of nutritional problems, whereby both undernutrition and overnutrition coexist in the same population.

Data sources

Estimates for all indicators were retrieved and reconstructed from data sources including the Ministry of Health of each respective country and drawn from different sources including the Organization of Economic Co-operation and Development (OECD) and the Food Agriculture Organization of the United Nations (FAO), LAMAC, and the World Bank.

REVIEW OF GOVERNMENTAL NUTRITIONAL POLICY

Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Brazil

Calorie-based undernutrition in children has been a public health issue in Brazil. Undernutrition was traditionally concentrated in families with the lowest income quintile and in the Northern region of the country. During the last few decades, however, Brazil achieved a gradual reduction in the prevalence of stunting and underweight in children starting in the late 1980s. The rate of reduction has accelerated in the 2000s particularly in the population segment traditionally affected the most by this nutritional problem. Based on the 2008-2009 Brazilian Household Budget Survey, the physical growth of children in the Northeast region no longer differs from what has been observed in all other regions of Brazil.[22] This reduction became more pronounced in the 2000s due to a series of governmental commitments, policy implementations, and increased spending to improve the general health of Brazilian citizens.[23] The 'Zero Hunger' strategy, implemented in 2003 by president Lula, is one example of Brazil's successful implementation of a nutrition policy to deliver a set of cost-effective interventions to the most vulnerable populations. Under this strategy, the Federal Government guaranteed the human right to adequate nutrition for impoverished citizens. Because childhood underweight is highly correlated with family food insecurity and poverty, the 'Zero Hunger' strategy integrated additional components such as expanding production and consumption of healthy foods, generating increased employment and income through job creation, and

improving universal educational services, which directly contributed to the reduction of the number of underweight children.[23] One of the key elements of success was Brazil's increased spending on nutritional improvement and poverty reduction through a conditional cash transfer program called the 'Family Basket.' Under this program, families living below the poverty line received direct income transfers by meeting conditions related to education and health.[24] Due to Brazil's current 6% annual rate of decline in the underweight prevalence in children, child malnutrition may be eliminated as a public health problem.[25]

Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Chile

In the case of Chile, about 40 percent of the population lived below the poverty line before 1990; however, as democracy was restored in 1990, the new government reinforced National Nutritional Supplement Program (*Programa Nacional de Alimentacion Complementaria)* and affirmed its commitment to improving health equality, including access to care.[26] Furthermore, the Chilean government integrated its nutritional policies through its educational system. For instance, Chile's National Nutritional Supplement Program (*Programa Nacional de Alimentacion Complementaria)* provided nutritious meals to children throughout the public school system, including nurseries, preschools, and in health centers across the nation. This level of full integration and coordination of the health system and public schools, along with political commitment, avoided duplication of efforts and inefficient use of resources. Through national coordination structures successfully aligned with social programs, Chile virtually

eradicated the prevalence of underweight children (under the age 6) by 2000: Based on the World Bank, the prevalence of underweight under 5 years old was less than 0.5 % in 2008. By constructing a comprehensive institutional base to address undernutrition, Chile demonstrated a reliable and successful model of sustainable economic and nutritional policies, which were initiated in the 1960s and have since been improved.

Government nutritional policy on reducing the prevalence of calorie-based undernutrition - Mexico

In Mexico, as in Brazil, a conditional cash transfer program was successfully implemented. In the *Oportunidades* cash transfer program, the Mexican Federal government targeted low-income households in both rural and urban areas, providing mothers with financial incentives for receiving preventive health care, nutritional education, and keeping their children in school.[27,28] By providing financial incentives to parents in exchange for their investment in their children's health and wellbeing, the *Oportunidades* program has had success in assisting family with children to escape the poverty chain as their children reach adulthood.[29] However, intra-national variation of the *Oportunidades* program remains further validation. In addition of the human capital development indicators (overall health, knowledge, nutrition, and skills), an independent and rigorous program assessment showed a positive effect on the nutritional status of these children with reduced prevalence of stunting and underweight.[30,31] The larger cumulative cash transfers showed correlation to increased height-for-age, decreased BMI, decreased prevalence of stunting and being overweight, and

increased performance on one scale of motor development.[27,31] However, prevalence of stunting in children under 5 years of age remains high (14%, 2010) and more comprehensive and targeted intervention to those at greatest risk may be needed to achieve objectives in the domain of optimal child growth.[32,33] Future study may explore differences between children from rural versus urban areas.

Synthesis, successful government nutritional policy on reducing the prevalence of calorie-based undernutrition

Our review provides examples of largely successful country-specific policies and programs and illustrates how these governments sponsored comprehensive policy and programs have benefitted their societies by reducing the prevalence of calorie-based undernutrition among children. One of the roles that governments can take to reduce nutritional disparities among children is to implement measures to improve access to food through safety nets or similar interventions promoting food availability. Such programs include integrated policy and programs such as cash transfer and cash-and-voucher schemes that target specific vulnerable population groups.[27,32,33] Initial results of these programs suggest that they can lead to higher caloric consumption and thus be obsesogenic. Further research is needed to exploit information in converging areas facing similar problems.

EMPIRICAL EVIDENCE OF IMPACT OF ECONOMIC GROWTH AND NUTRITIONAL CHANGES

Trends of gross national income: comparison among Brazil, Chile, and Mexico

Figure 2 illustrates each country's economic growth and the associated changes in undernutrition, vitamin A deficiency, and overweight/obesity in

children under five years of age. The Gross National Income (GNI) per capita in Brazil, Chile, and Mexico grew an average of 17 percent annually from 1990 to 2010. For instance, in 1990, all three countries started their GNI ranging from $2,240 to $2,740 in US$. (All values expressed in U.S. dollars). By 2010, the GNI grew significantly to values ranging from $8,700 to $10,700. Growth rates for all three countries were more rapid in the 2000s than in the 1990s, with the most dramatic growth taking place in Brazil. The resulting increase in capital between 1990 and 2010 allowed the Brazilian government to reduce its overall external debt and accumulate a massive amount of reserves.[34] In all three countries, average household income grew during the mid-2000s, not only because of economic growth and increased opportunities for employment, but also because the real minimum wage started to grow at the same time.[5]

Synthesis, impact of economic growth on child nutritional outcomes

Economic growth in recent decades has been a powerful force for reducing calorie-based undernutrition; however, the number of children with micronutrient deficiencies remains high and widespread throughout Latin American countries with a prevalence greater than 10%. This indicates the complex nature of maintaining optimal nutritional status. Moreover, economic growth and increased individual purchasing power has unfortunately been accompanied by a simultaneous increase in overweight/obesity in children less than five years of age. The increasing trend of obesity is clearly depicted in Chile. In the most recent nutritional status report among children under 5 years of age,

the total prevalence of overweight and obesity is 50 % in 2013 (data not reported).[35]

This initial evidence may lead one to conclude that economic growth is directly linked to decreasing malnutrition and to increasing obesity; however, nutritional disorders result from multiple causes, and require further analyses that take into consideration the complexity of the phenomenon. Below we address these multiple causes using underlying and immediate factors of malnutrition.

Trends of food availability and the quality of diets on child nutritional outcomes

Indicators of change and supply of quality diets may have more direct correlation with nutritional outcomes among children. In fact, with an average 17 percent annual increase in per capita income between 1990 and 2010, all three countries demonstrated an increased trend of food energy and nutritional availability (Fig 3). The link between economic growth and nutrition transition based on the sufficient food availability (average dietary supply adequacy) validates the fact that economic growth and nutrition transition happen simultaneously. Among the three countries, Brazil showed the largest absolute increase in demand for food more than adequate, while Mexico showed the smallest. Over the last two decades, food supplies have grown faster than the population in all three countries, indicating a nutrition transition from food insecurity to security. Indeed, supplies of dietary energy have risen faster than average dietary energy requirements, resulting in a net excess of calories for all three countries (>100%).

Synthesis, impact of nutritional changes on child nutritional outcomes: comparison among Brazil, Chile, and Mexico

The increase in food availability has been accompanied by changes in dietary composition. Figure 3 illustrates dietary changes that occurred in each of the 3 countries from 1990 to 2010. These data are examined in terms of shares of major food groups consumed, including fruits, meat, and vegetables. We find a notable increase in the per capita supply in dietary energy from meat, while fats derived from animal, fruits, and vegetables remain essentially constant. Increased per capita income along with dietary changes are related to major nutritional changes in all 3 countries. We noted a high correlation coefficient between GNI in Brazil, Chile, and Mexico with availability of meat (correlation coefficients ≥ 0.67 for all 3 countries). The per capita increase in the availability of meat is consistent with improvements in economic access to food, which is reflected in the reduction of the prevalence of undernutrition and stunting in children under five years of age over 20 years. Furthermore, the per capita availability of fruits and vegetables seem to remain consistent with the persistent level of prevalence in certain type of micronutrient deficiencies over time. The overall demand of fruits and vegetables may be lower than the demand of meat. This uneven dietary development provides evidence of the coexistence of undernutrition and overnutrition among children depicted by the persistent prevalence of children with micronutrient problems and increasing trends of childhood obesity.

Evidence of correlation between increased sedentary behavior and child obesity: comparison among Brazil, Chile, and Mexico

Currently, we do not have reliable information about the life style risk factors (e.g. reduced physical activity). In this study, we used the rise in pay TV subscriptions, which its trend is consistent with an increased trend of childhood obesity. Studies suggest that TV watching places individuals at elevated risk of obesity independent of lowered physical activity levels.[19,20,36] The rise in pay TV subscriptions gives additional observation of behavior changes that individuals make with economic growth. The Latin America Consumers Report 2020 provides evidence that increasing income lead consumers to purchase appliances, automobiles, and other electronics, such as computers and TVs, which have shown to be contributing risk factors for obesity through the promotion of sedentary behaviors.[20] The change toward increased sedentary lifestyles is a strong predictor for the increasing risk of obesity. The latest report from the LAMAC partly confirms the changes of consumers' behavior by presenting a set of comparisons of computed probabilitiy of pay TV subscribers having automobiles of computers/tablets when compared to those without pay TV.[37] The change of consumers' purchasing behavior and pattern are beyond the score of this review.

DISCUSSION: DUAL BURDEN CHALLENGES

In review of largely successful policies and strategies undertaken by each country to reduce the prevalence of calorie-based undernutrition, we found political momentum, inter-institutional coordination structures, and alignment of

social programs with a national nutritional strategy to be the most important elements for reducing the prevalence of underweight children. However, most of successful policy integration and nutrition based programs have focused on one-nutritional-disorder-at-a-time (e.g. lowering prevalence of calorie-based undernutrition); we are not aware of equally successful programs and elements for addressing the other two nutritional statuses simultaneously (e.g. micronutrient deficiency and obesity). For micronutrients, innovative and successful fortification and supplementation programs are available, but addressing childhood obesity has been notoriously difficult and remains an ongoing challenge for all three countries. Research shows that unhealthy dietary habits and physical inactivity are the main risk factors driving the onset of obesity.[19,36] Many experts agree that intervention at an early age, before life habits are formed, is key to slowing the rate of childhood obesity in Latin America. However, there is no evidence that the three countries have had success in intervening with childhood obesity at early age. The challenge remains as the prevalence of obesity continued to increase and there is no easy solution to this complex nutritional disorder.

We present a case study of Chile to illustrate that interventions of one-nutritional-disorder-at-a-time may not address the broad-spectrum and the complexity of childhood obesity. Chile is the first country in Latin American to achieve eradication of underweight in children, and has set an exemplary model of addressing certain types of micronutrient deficiency (prevalence of iron deficiency anemia in infancy). However, despite the Chilean government's efforts

to mitigate the problem, to date, childhood obesity has remained relatively intractable. For instance, having noted the nutrition transition in Chile, the Ministry of Health changed its traditional maternal and child policies in 1998, giving high priority to mitigating chronic diseases and obesity. The Chilean government adopted similar strategies to cope with obesity at preschool facilities through integrating its nutritional policy into its educational system. With the change in focus from prevention of undernutrition to prevention of obesity, the school food program emphasized including healthier and less caloric foods in the diet, such as fruits and vegetables 10 times a week, fish and legumes twice a week and skim milk every day, as well as decreasing saturated fats, sugar and salt in school lunches and breakfasts. Despite these changes and continued monitoring, obesity rates did not decrease. In fact, contrary to expected results, the prevalence of obesity among school-aged children actually increased. The trend in childhood obesity is now similar to that in the United Kingdom and the United States.[38] The greater challenge is that, in general, the population knows what healthy eating means and understands the benefits of engaging in physical activity, but many people persist in eating foods that are high in sugar and fat and leading inactive lives despite this knowledge. As in the United States and elsewhere, it is clear that knowledge is necessary but not sufficient in order to promote behavior change and reduce the risk of obesity. Greater attention needs to be placed on environmental changes (e.g., public spaces that promote exercise) and behavior modification in order to reduce unhealthy dietary

practices and sedentary behaviors, and on understanding factors beyond knowledge that shape these behaviors

CONCLUSIONS

Our review provides examples of nutritional policy implementation along with empirical evidence of linkages between economic growth and child nutritional indicators through several pathways in three Latin American countries. This novel approach contributes to improved understanding of the effort to reduce the burden of nutritional disorders through an added understanding of its complexities and interconnectedness.

Government policy and programs have an essential role in facilitating a conducive economic environment for the shift of secular nutrition trends to happen by increasing the food availability and making access to quality foods easier for all people. However, by reviewing successful cases of addressing undernutrition and ongoing challenges of addressing overnutrition, we learned that no matter how successful a policy integration and nutrition based programs have been, interventions of one-nutritional-disorder-at-a-time cannot address the co-existence of broad-spectrum of nutritional disorders. Acknowledging the complex nature of maintaining optimal nutritional status, important conceptual and practical work remains to be done in developing national initiatives and improving inter-institutional coordination to make policies more effective and sustainable within each country's context.

By reviewing specific indicators of the dual burden of nutritional changes in the context of economic transition, our study contributes important and useful

information to the comparisons of childhood undernutrition and obesity among Latin American countries in transition. The empirical evidence presented in this study identified that higher levels of per capita income appear to reduce the proportion of the population who suffer from insufficient food energy intake. The increasing trends in per capita income and food availability are consistent with decreasing trends in calorie-based undernutrition and increasing trend of excess nutrition. Moreover, we presented evidence of the intended and unintended consequences of economic growth on children's nutritional status through several pathways. Lastly, we presented pay TV subscription data as an indicator to express the increasing trends of sedentary behavior, which may contribute to the increasing prevalence and persistence of childhood obesity in all three countries.

For future directions to address global health challenges related to under and over nutrition among countries undergoing similar economic transition, we suggest using a framework explicitly presented in the Global Goals Global Goals for Sustainable Development (SDGs) for the post-2015 agenda to transforming the world.[39-42] The SDGs presents an interwoven set of global priorities built upon the unfinished business of the Millennium Development Goals. In these synergistic, mutually supportive and equal priority goals, nutrition plays a role as both an input to, and an outcome of, the SDGs as a whole. For instance, problems of malnutrition derive from a synergistic effect of lack of sufficient and adequately nutritious food being linked with health, care, education, sanitation, and access to resources and more. On the other hand, good nutritional status

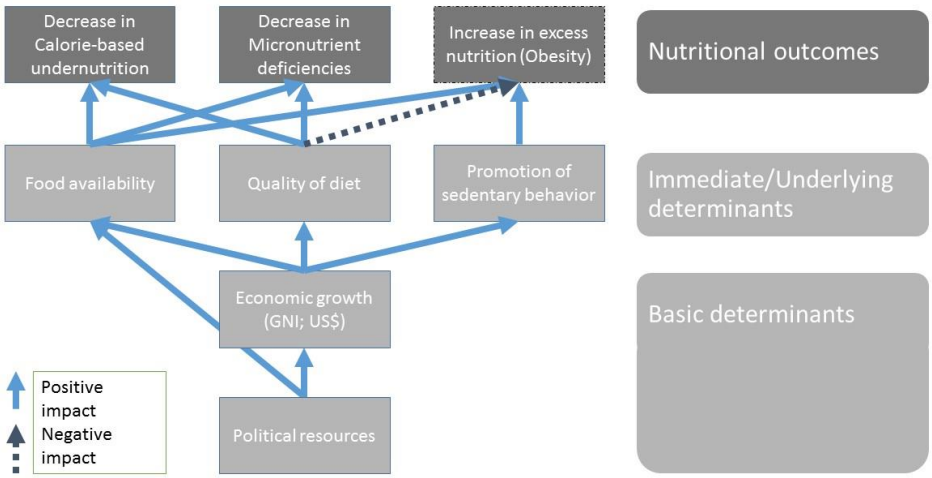
leads to higher individual earning and mental acuity, which in turn support country's macroeconomic and societal growth.

By messaging how nutrition can play a key role in promoting achievement of the various SDGs, and how achieving the SDGs can also benefit nutrition, the recommendation of future policies and programs must consider these multidirectional linkages between nutrition and the SDG targets. With the acknowledgment of the multifaceted nature of nutrition, where 'nutrition' is about more than the absence of one visible or invisible form or manifestation of nutrient deficiency or being too heavy, the future national initiatives and inter-institutional coordination would be benefitted by promoting healthier economic and societal development while integrating nutrition-relevant indicators in each initiative and project.

As many countries in Latin America and other parts around the world are at a stage of the economic and nutrition transition, lessons learned from our study through trend analyses of publicly available data, as well as review of successful cases and ongoing challenges, have the potential to inform effective and sustainable prevention efforts in other global settings.

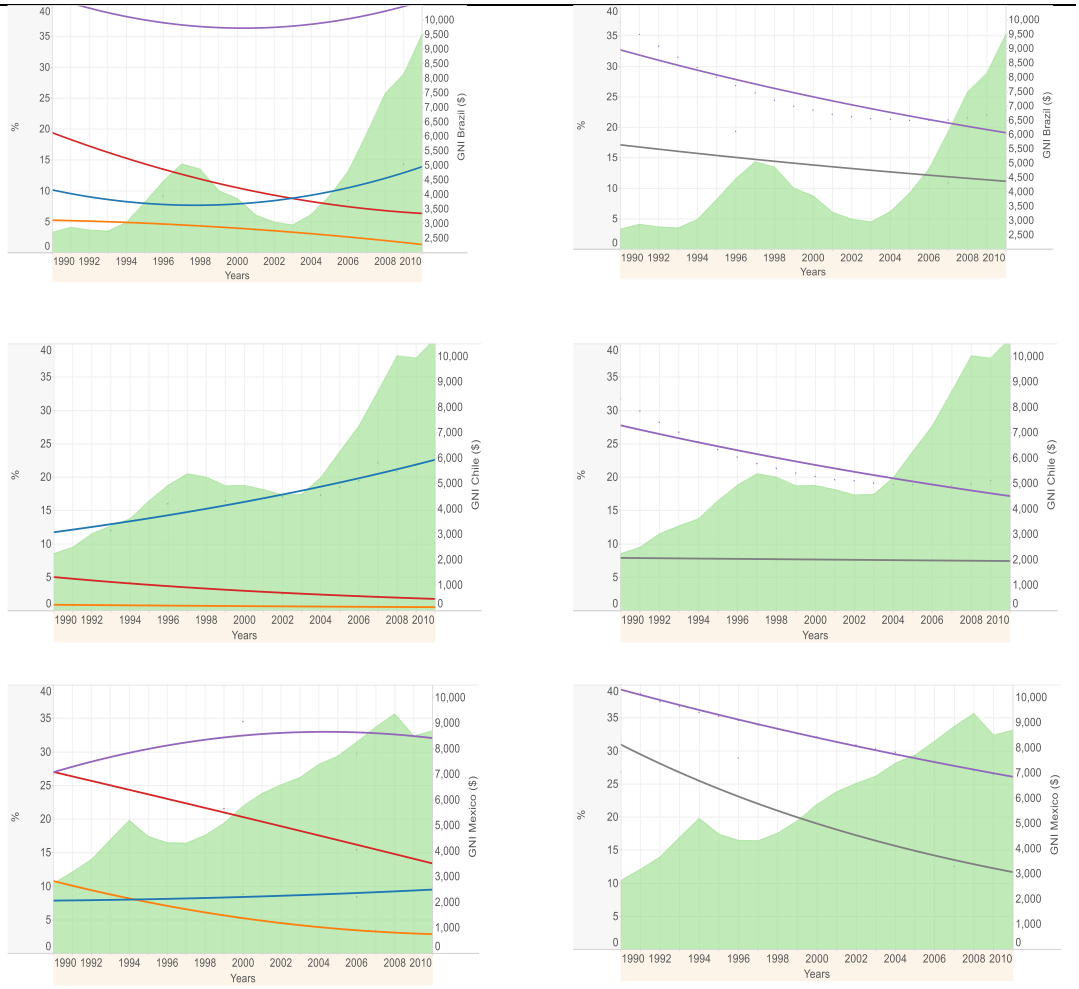
ACKNOWLEDGEMENTS

Chapter 2, in full, will be submitted for publication of the material as it may appear in the *Public Health Nutrition*: Kang Sim D, Gallo L, Zúñiga ML, Gahagan S: The impact of economic growth and nutritional changes on the burden of undernutrition and obesity in children in Brazil, Chile, and Mexico. D. Eastern Kang Sim was the primary investigator and author of this paper.



Adopted from the UNICEF conceptual framework of malnutrition

Figure 2.1. Conceptual framework linking economic development, food supply, behavioral pattern, and nutritional status



Stunting = red (FAOstat)
Undernourishment = orange (FAOstat)
Overweight/obesity = purple (Ministry of health/ WHO)*
Obesity = blue (Ministry of health)
Gross National Income = green area (World Bank)
*No repeated overweight+obesity prevalence was reported for Chiilean children under 5 years of age. Data from the 2013 report, however, shows 50% of children under 5 years of age fall into overweight/obesity category.

Anemia = purple (FAOstat)
Vitamin A deficiency = grey (FAOstat; % of population)
Gross National Income = green area (World Bank)

Figure 2.2. Trend lines of calorie-based nutrition and micronutrient indicators with gross national income from 1990 to 2010

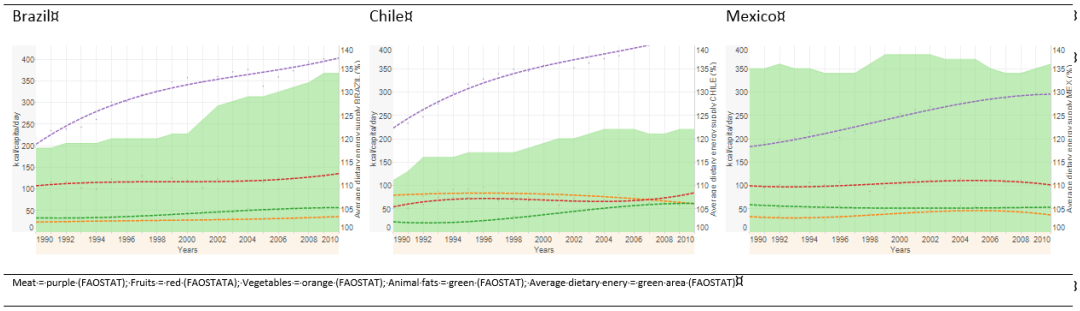
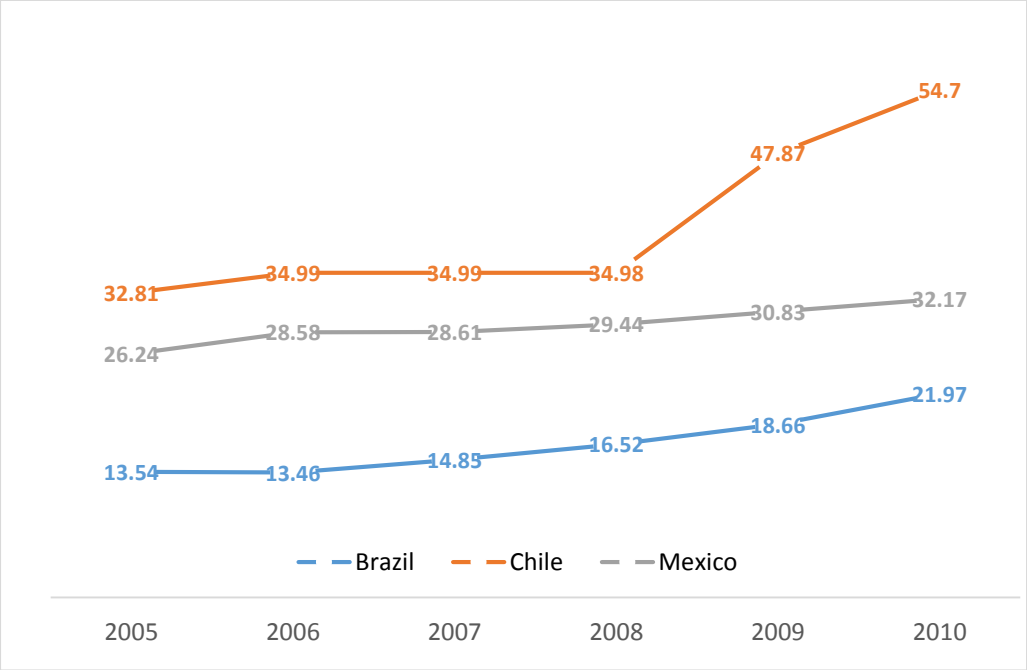


Figure 2.3. Trend lines of quality and supply of food with per capita food availability from 1990 to 2010



Source: LAMAC

Figure 2.4. Changes of market penetration of TV service subscription in Brazil, Chile, and Mexico from 2005 to 2010

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CHAPTER 3: THE IMPACT OF INFANT IRON DEFICIENCY AND ADOLESCENT OVERWEIGHT STATUS ON NEUROCOGNITIVE PERFORMANCE DURING ADOLESCENCE: A TEST OF TWO-HIT NUTRITIONAL INSULT HYPOTHESIS

ABSTRACT

The timing and impact of nutritional insults during critical child developmental periods have long been recognized as significant factors in deficient neurocognitive functioning. As nutrients often act synergistically, it is plausible that the joint occurrence of iron deficiency and iron deficiency anemia (ID/IDA) during infancy along with overweight/obesity (OW/OB) in adolescence has an independent adverse effect on neurocognitive functioning, in particular with reaction times and accuracy, greater than that experienced with either condition alone. This study examined the potential incremental risk associated with exposure to two independent nutritional insults during sensitive developmental periods, as opposed to one or no exposures.

Data were examined from a longitudinal cohort study of Chilean infants who participated in a randomized controlled trial to prevent iron deficiency anemia. We analyzed data from the Stroop computerized task that assessed individuals' reaction time and accuracy, which can be a measure of cognitive functioning. Infant iron status was assessed at 6, 12, and 18 months, and the Adolescent BMI percentile was computed using CDC norms. Marginal means were estimated while adjusting for covariates. Adolescents who experienced ID/IDA in infancy and OW/B in adolescence showed significantly longer reaction times (B=107.12; 95% CI: 23.28, 190.95; $p < .05$; 1021 msec) on the Stroop task

compared to adolescents who were OW/OB alone (B=17.36; 95% CI: -31.75, 66.49; 931 msec), ID/IDA alone (B= 28.92; 95% CI: -33.80, 91.65; 950 msec), or had neither condition (reference category; 911 msec). There were no significant differences in accuracy between the groups.

Findings show that joint exposure to ID/IDA and OW/OB is associated with slower response time, while ID/IDA and OW/B alone were not associated with declines in performance.

Keywords: Iron deficiency, iron deficiency anemia, overweight, obesity, adolescence, neurocognitive functioning, nutritional insult

INTRODUCTION

The timing and impact of nutritional insults (i.e. periods of nutritional conditions that adversely affect physical and mental health) during sensitive developmental periods in children have been recognized as critical in neurocognitive development and functioning.[1-3] During infancy, iron deficiency and iron-deficiency anemia (ID/IDA) have been shown to affect brain-circuit development.[3-7] Because infancy is a period of rapid brain growth during which critical iron-containing hemoproteins are needed for hippocampal and cortical regional development, iron deficiency during infancy can have serious and long-lasting effects on subsequent cognitive and socioemotional functioning[5,8,9] Adolescence is another sensitive period that marks significant changes in the brain second only to that seen in infancy.[10-12] Although the underlying mechanisms regarding how obesity detrimentally affect health remains unclear, increased inflammation due to obesity during adolescence has been associated with the cognitive impairment. For example, epidemiological studies have reported deficits in learning, memory, executive functioning in obese as compared to non-obese participants.[13-15] Regression studies suggest increased body mass index (BMI) was inversely associated with decreased brain volume and lowered performance level on the Stroop Color-Word Interference Test, a measure of brain processing speed and accuracy.[16] The finding suggests that brain inflammation due to the degree of obesity in adolescents may diminish myelination and synaptic efficacy, which impact brain processing and functioning.

Given that a majority of studies investigating the link between nutritional insult and cognitive development have mainly focused on one developmental period (e.g., infancy only), or an individual nutrient or diet, there is a gap in research on potential synergistic effects of greater than one nutritional insult at different developmental periods on cognitive outcomes. In other words, most studies have examined the risk of adverse cognitive functioning associated with either ID/IDA or overweight/obese (OW/OB) at onetime point. As the availability of, or lack of access to, nutrients often contributes to brain performance, it is plausible that a 'two-hit' insult, such as the presence of ID/IDA in infancy with OW/OB in adolescence, may negatively impact cognitive functioning more than either condition alone. In general, the two-hit insult model can be explained where an early-life disruption (first-hit) produces a long-term vulnerability to a second-hit insult, which in turn leads to increased risk to adverse health outcomes. The characteristic of the two-hit insult underlies that neither insult by itself is sufficient to cause adverse outcome. Drawing from a longitudinal cohort study with Chilean children, we hypothesized that adolescents with two-hit insults; that is, with both ID/IDA in infancy and OW/OB in adolescence, would demonstrate lower levels of cognitive functioning (reaction times and accuracy) than those with either ID/IDA or OW/OB or neither condition.

METHODS

Study design and participants

Participants were part of a longitudinal study of infant iron deficiency anemia (IDA) preventive trial in Santiago, Chile from 1991 to 1996. The original

cohort consisted of 1657 healthy, full-term Chilean infants who completed a randomized, controlled trial of iron supplementation to prevent iron deficiency anemia. [17] In brief, the initial prevention trial was conducted in four low- to middle-income communities in Santiago, Chile. Non-nutritional causes of anemia were essentially nonexistent.[18] All participants were from single, term births with healthy birth weights greater than 3 kilograms, and with no known perinatal complications. At 6 months, all infants were screened for iron status via a finger prick and received an additional venipuncture at 12 and 18 months for follow-up determination of iron status. As part of their participations, study participants were given weekly supplement of formula and regular pediatric care. Participants completed follow-up measures and were assessed for adverse developmental outcomes at 5, 10, and 16 years of age. At 16 years, participants also underwent a neurocognitive assessment.

For the present study, we utilized the iron data collected at infancy (6, 12, and 18 months) to determine iron deficiency status and BMI data at adolescence (16 years) to determine overweight/obesity (OW/OB). Among 147 participants who received a complete computerized cognitive assessment at adolescence, 116 participants had all variables of interest at infancy and adolescence. These participants formed the core analytic sample for the current study. No significant differences were noted on sociodemographic indicators between participants with complete data and excluded in the analysis due to missing data. The study protocol was approved by Institutional Review Boards at the University of Michigan, the University of California, San Diego, and the University of Chile.

Measures

Dependent variable: Cognitive performances

A variant of the Color-Word Stroop computerized task was used to assess cognitive performance, specifically in reaction times and accuracy.[19] In this task, participants must identify the ink color for a printed word while ignoring the meaning of the printed word. Performance was assessed in reaction time (msec) and accuracy (%). The task includes two trial types, incongruent and neutral. For incongruent trials, the word presented (e.g., RED) was in conflict with the ink color with which it was printed (e.g., BLUE). In contrast, the words used for the neutral trial did not present any color information and therefore did not conflict with the meaning of the printed word. In the unequal block, participants completed 36 neutral trials and 12 incongruent trials. The incongruent trial in unequal block is known to be more sensitive to differences in the ability to implement attentional control. **[19]**

Iron deficiency status in infancy

Iron deficiency status was assessed at 6, 12 and 18 months, and was defined as 2 out of 3 iron measures within the deficient range (mean cell volume < 70 fl, erythrocyte protoporphyrin >= 1.77 uM red blood cells and serum ferritin < 12 ug/L) at any onetime point in infancy. Iron deficiency anemia (IDA) was defined as venous hemoglobin <= 100 g/L at 6 months and <110 g/L at 12 and 18 months.[20] Infants who were ID or IDA at any onetime point in infancy received a code of ‘1’ or ‘ever ID/IDA’ while those who were iron sufficient received a code of ‘0’.

Weight status in adolescence

Height and weight were measured while individuals were in light clothing and without shoes in the Nutrition Research Center. Measurements were obtained using a digital scale (0.1 kg) and a stadiometer (0.1 cm precision) according to standardized methods. Body mass index (BMI= kg/m^2) was calculated and translated to a BMI percentile according to CDC norms, then the resulting percentile was used to classify the overweight/obesity (OW/OB) category (BMI p>= 85^{th} percentile).[21]

Two-hit exposure

Two-hit exposure was defined when individuals were exposed to a 'two-hit' nutritional insult of ID/IDA in infancy first and OW/OB in adolescence second.

Covariates

As stimulation environment and toxic stress influence cognitive functioning, we included quality of the nurturing environment at home at infancy[22] (measured using the Home Observation for Measurement of the Environment; score range: 18-41), and the chaotic environment of the home at adolescence (e.g., the level of noise, crowding and confusion in the home as measured by the CHAOS; score range: 16-27).[23] Other covariates included age at adolescence, sex, and birthweight (a proxy for socioeconomic status in infancy). Randomization in the iron preventive trial (iron supplementation versus no supplementation) was not related to any of the study variables, and thus is not considered further.

Statistical analyses

Statistical analyses for this study were conducted with data from 116 participants using the SAS Systems for Windows (version 9.3, SAS Institute, Inc, Cary, NC) and SPSS (version 21, IBM SPSS Statistics, IBM Corporation). Values for descriptive statistics were shown as means and standard deviations or percentages. Multivariate regression models were used to estimate the marginal means of the two-hit effect of the ID/IDA and OW/OB. The bias-corrected and accelerated (BCa) bootstrap procedure was used to obtain standard errors and confidence intervals.[24] Lastly, we assessed attributing effects associated with a two-hit nutritional insult by identifying which subgroups of the two-hit nutritional insults (ID/IDA or OW/OB) were contributing to the estimated effect.[25]

RESULTS

Sample characteristics

Sociodemographic participant data are provided in Table 1. Among the 116 participants who had complete data, 20% of the participants was iron deficient or had iron-deficiency anemia (ID/IDA) in infancy, and 33% participants was overweight or obese (OW/OB) in adolescence. The average reaction time on the Stroop task was 931.9 (SD 119.3) msec with 81% accuracy.

Stroop reaction times and accuracy

In our final regression model, differences in the reaction time were noted for ‘ever ID/IDA’ alone (B= 28.92; 95% CI: -33.80, 91.65) and OW/OB alone (B=17.36; 95% CI: -31.75, 66.49) compared to the healthy control group, but the effect of a single exposure (either ‘ever ID/IDA’ or ‘OW/OB’) was generally small

and not statistically significant (p>0.05). Participants who were jointly impacted by ‘ever ID/IDA’ and OW/OB showed a large, statistically significantly longer average reaction time (B=107.12; 95% CI: 23.28, 190.95; p < .05) compared to the healthy control group. Differences in the accuracy were nominal for a single exposure (B=-0.01, -0.04; both p>0.05), but two-hit exposure was related to a marginally significant drop in accuracy (B=-0.11; p>0.05). Figure 2 shows the covariate-adjusted means (CM) of the Stroop reaction times and accuracy. Adolescents who experienced ID/IDA in infancy and were OW/OB in adolescence showed significantly slower reaction times (CM: 1021.30 msec) and diminished accuracy (74%) on the Stroop task compared to adolescents with OW/OB alone (CM: 925.69 msec; 81%), and ID/IDA alone (CM: 937.24 msec; 84%), or with neither condition (CM: 908.32 msec; 85%). The difference of the Stroop accuracy scores was marginally statistically significant (p=0.06) between those who had experienced Two-hit exposure and those who had experienced neither exposure.

Attributable effects of the Two-hit effect

In regard to Two-hit exposure, almost one quarter of the joint effect was due to the effect of ID/IDA in the absence of OW/OB. Approximately 35% of the effect was due to OW/OB in the absence of ID/IDA, and approximately 40% of the joint effect was due to the interaction between ID/IDA and OW/OB.

DISCUSSION

This study provides evidence that Two-hit exposure to ID/IDA in infancy and OW/OB in adolescence is associated with longer reaction times, whereas

exposure to either ID/IDA or OW/OB alone was not related to a reduction in our indicators of cognitive performance.

The impact of perinatal iron deficiency on cognitive development is of particular interest because the growth spurt that takes place during the first 2 years after birth is due to dendritic growth and synaptogenesis.[7] Iron deficiency during this critical period has a direct negative impact and alters cognitive development. For this study, 2 of 3 abnormal iron measures were used to define iron deficiency and accurately capture the iron status of infancy. The resulting data demonstrate that there is no difference in cognitive performance between normal weight adolescents with ID/IDA in infancy compared to the healthy control group. Because we observed an additive interaction between ID/IDA and OW/OB, it is plausible that the reorganization of brain-circuit architecture and maturation that occurs during adolescence may provide a window of opportunity to mitigate the adverse effects of iron deficiency.

Adolescence is another sensitive period for structural reorganization of the brain and there may be a delay in crucial memory searching processes and reorganization of neural circuitry for OW/OB adolescents without ID/IDA in infancy when compared to their healthy counterparts. This study found no association between OW/OB status and indicators of cognitive performance. The fact that this study demonstrates that a single-hit nutritional insult was not associated with indicators of cognitive performance suggests that continuing brain maturation and proper stimulation in adolescents may provide some degree of adaptive brain plasticity that minimizes the differences in the reaction

time, which may bring a beneficial effect on cognitive functioning later in life. For individuals with Two-hit exposure, also known as ‘two-hit’ exposure, to ID/IDA in infancy and OW/OB in adolescence, the adverse effect on synapses appears to lead to less processing speed during adolescence, which may be due to a synergistic disruption of critical steps in brain development and reorganization during sensitive periods.

Public health implication

Infant iron deficiency remains one of the most prevalent conditions of undernutrition in low-and middle-income countries, and the adverse consequences are of high public health concern. With increased caloric intake and globalization of the food system, many children who were at risk of iron deficiency in their early years are also at risk of obesity later in life. Our study findings revealed that the Two-hit impact of these two common nutritional insults may leads to greater cognitive deficits. Although additional research is needed, it is plausible that this additive effect in adolescence could contribute to later socioeconomic disparities into adulthood. Studies suggest that cognitive deficits are associated with decreases in mental health, academic success, social function, and economic success in the impacted communities.[26] Two-hit nutritional insults may be exacerbated in transitioning countries where the shift in nutrition profiles has taken place rapidly as members of the societies experience the intended benefits and unintended consequences of economic growth.[27]

From a public health perspective, one motivation for studying the two-hit hypothesis is to identify which subgroups (e.g., ID/IDA or OW/OB) would most

benefit from intervention for nutritional insults when resources are limited or not feasible. For instance, it may not possible to directly intervene on OW/OB in a resource-limited setting. In this case, one might instead be interested in reducing the adverse effect of ID/IDA in cognitive performance later in life. The estimation method we implemented in the current study can provide additional information and be an easier measure to interpret for assessing the synergistic effect on cognitive performances. Our study indicated that 40% of longer reaction times were due to the Two-hit exposure of both conditions, whereas ID/IDA in infancy attributed about 25% of the effect. This implies that the combination of ID/IDA and OW/OB explains a significant portion of the decrease in cognitive performance, but also implies that by preventing iron deficiency in infancy alone, a significant portion of the synergistic effect can be averted.

Limitations and future studies

This study examined infancy and adolescence as two sensitive periods for brain development, and excluded childhood and young adulthood. Examination of nutritional insults that occurred earlier (i.e., prenatal period) or later (after physical maturation is largely complete) might well have shown different effects. Moreover, studies are inconclusive in terms of directionality between obesity and cognitive dysfunction. It is possible that low levels of cognitive functioning are a risk factor for an increased BMI in adolescence. However, the directionality of the relation between obesity and cognition is difficult to determine given that most studies analyze obesity status in an isolated time point. This study contributes to the existing literature by including two developmentally sensitive periods. More

research is needed in this area to better understand the directionality and magnitude of this association between a ‘two-hit’ nutritional insult and individual cognitive functioning.

Conclusion

Understanding the adverse outcomes of a two-hit insult during key developmental periods is imperative to designing effective interventions aimed at mitigating adverse effects in brain development and performance. Given the consequences of developmental delays in cognitive function, strategies to prevent poor iron status during key developmental periods and obesity warrants more attention. Together, the evidence suggests that adequate nutrition from birth to adulthood is necessary for optimal cognitive development.

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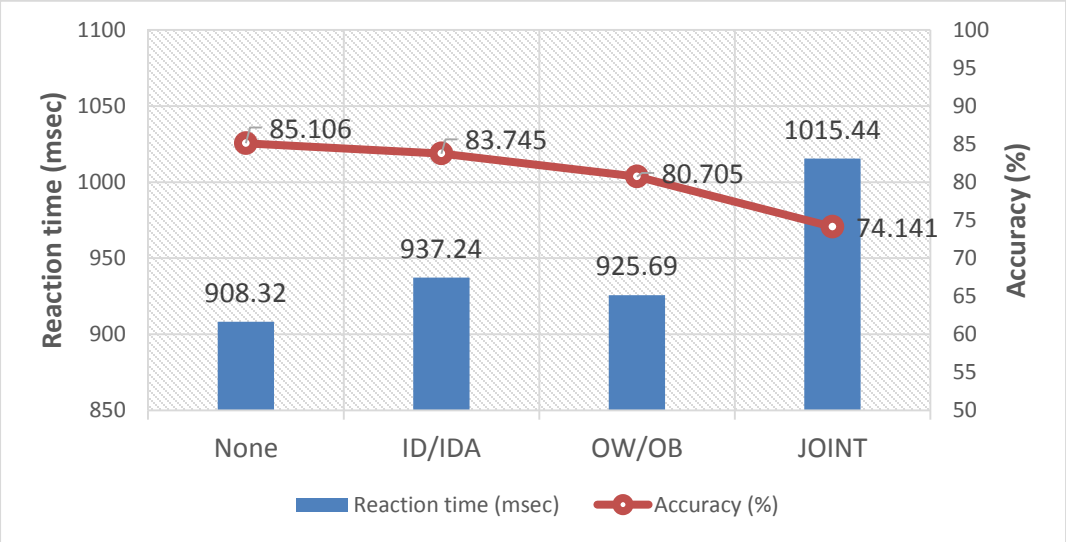
Table 3.1. Characteristics of participants

Variables	n (%) or mean (std dev)
Reaction time (msec)	931.90 (119.27)
Accuracy (%)	94 (81%)
Ever iron deficient or anemia in infancy (ID/IDA)	24 (21%)
Overweight and obese in adolescence (OW/OB)	40 (34%)
Male	58 (50%)
Age in adolescence	16.28 (0.84)
Birthweight (gram)	3515.37 (377.16)
Infancy SES (range: 16-47)	28.13 (6.18)
HOME in infancy (range 18-41)	30.05 (4.97)
CHAOS in adolescence (range 16-27)	22.33 (1.61)



Adjusted for sex, age in adolescence, birthweight, SES in infancy, HOME in infancy, and CHAOS in adolescence.

Figure 3.1. Covariate-adjusted means of reaction time (msec) and accuracy (%) by nutritional insult status

Table 3.2. Regression coefficients and attributable proportion

Variables of interest (ref. no nutritional insult)	Beta	BCa 95% Confidence Intervals	p-value
[Reaction times]			
ID/IDA in infancy	28.92	(-33.80, 91.65)	0.36
OW/OB in adolescence	17.36	(-31.75, 66.49)	0.49
Joint effect	107.12	(23.28, 190.95)	0.01
[Accuracy]			
ID/IDA in infancy	-0.01	(-0.10, 0.07)	0.71
OW/OB in adolescence	-0.04	(-0.136, 0.04)	0.24
Joint effect	-0.11	(-0.24, 0.03)	0.06

Adjusted for gender, age in adolescence, birthweight, SES, HOME in infancy, and CHAOS in adolescence.

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CHAPTER 4: THE ADDITIVE IMPACT OF INFANT IRON DEFICIENCY AND ADOLESCENT OVERWEIGHT STATUS FOR YOUTHS' EXTERNALIZING PROBLEM BEHAVIOR: TESTING A TWO-HIT NUTRITIONAL INSULT HYPOTHESIS

ABSTRACT

Objective: The purpose of this study was to assess the additive impact of iron deficiency in infancy and overweight/obesity in adolescence for externalizing behaviors in adolescence.

Methods: Data were from a large, longitudinal study of Chilean infants who participated in a randomized controlled iron deficiency preventive trial. Infant iron deficient status was assessed by venipunction at 6, 12, and 18 mo., and adolescents' body mass index percentile were computed using CDC norms. Self-ratings on the Achenbach Youth Self Report assessed externalizing problems. We calculated index of multiplicativity and additivity. For analyses concerning index of multiplicativity, logistic regressions were used and adjusted for covariates. Indices of additivity were estimated using linear binomial regression and other indices including relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S).

Results: Adolescents who experienced a two-hit insult of iron deficiency in infancy and overweight/obesity during adolescence showed 67% increased odds of exhibiting externalizing behavior problems at age 16. A positive deviation from additivity (β=0.10; RERI= 1.4; S=2.9) and multiplicativity (OR= 1.7; 95% CI: 1.1, 2.7) on youth externalizing behavior problem were found. There was no

significant association between either condition as a single-hit exposure and externalizing problem behaviors.

Conclusion: A two-hit insult of iron deficiency and overweight/obesity showed a significant additive and multiplicative effect for externalizing problem behavior beyond having either condition alone. The two-hit nutritional insult concept proved useful in understanding the additive effects of two different nutritional insults and warrants further application.

Keywords:

Iron deficiency, Adolescence, Externalizing problem behaviors, two-hit nutritional insult, overweight, obesity

INTRODUCTION

Because of its influence on enzymes, neurotransmitters, neurogenesis, and synaptic plasticity, nutrition is one of many environmental factors that profoundly impacts brain development and functioning during infancy and adolescence.[1-3] During infancy, trace elements such as iron are particularly important due to their essential role in neuro-circuit development, and a deficiency can result in permanent damage in brain functioning even after repletion.[1-3] There is strong evidence that iron deficiency during infancy may result in cognitive deficits and increased risks for externalizing behaviors in adulthood.[4,5] Likewise, adolescence is a critical and sensitive period of renewal and remediation through neural plasticity, second only to that seen in infancy, and nutritional deficiencies and excesses during adolescence may have larger adverse effects on cognitive dysfunction and increased frequency of risk-taking behavior compared to such risk-taking behaviors observed in childhood.[6-8] Studies suggest that the steep increases in frequency and chronicity of adolescent's behavioral difficulties can be explained partly by diminished self-control and the inability to suppress risky behaviors as a result of poorer ability to process inhibition and responses to social information.[9,10] Although the exact mechanisms remain unclear, studies suggest that chronic inflammation due to adolescent obesity may have a detrimental effect on brain plasticity and inhibitory skill, which in turn can increase the likelihood of individuals exhibiting adverse brain-behavior manifestations.[11,12]

A majority of studies investigating the link between nutritional insults and adverse behavioral manifestations has examined nutritional insults during only one developmental period or examined only one nutritional insult at a time. There is a gap in knowledge about the potential impact on behavior resulting from nutritional insults experienced during two developmentally sensitive periods. With the brain as the primary determinant of behavior problems and nutrition as a source of susceptibility, it is plausible that the damage caused by infant iron deficiency along with being overweight or obese during adolescence may put individuals who are exposed to both conditions at a greater risk for behavioral difficulties relative to experiencing either conditions alone. We hypothesize that adolescents who were exposed to iron deficiency or anemia (ID/IDA) in infancy and were overweight or obesity (OW/OB) in adolescence would demonstrate a higher risk for externalizing behavioral problems than adolescents with either condition alone, or adolescents without these conditions.

METHODS

Study site

The current study was conducted in low-to-middle income communities in Santiago, Chile. Although moderate-to-severe cases of infant iron deficiency anemia were of significant concern when this study was undertaken in the early 1990s, infant iron deficiency anemia is now essentially eliminated due to Chile's improved economy and the impact of country-wide nutrition education.[13-15] However, with the improved economy, Chile went through nutrition transition,

resulting in a high prevalence of obesity problems.[14,16-18] The trend in childhood obesity is now similar to those in the United Kingdom and the United States.[19]

Design and sampling

Participants were recruited for an infant iron deficiency anemia preventive trial in Santiago, Chile from 1991 to 1996. The Institute of Nutrition and Food Technology, University of Chile enrolled 1657 participants at age 6mo and followed them to 18mo during infancy. Participants were then followed at age 5yo, 10yo, and adolescence (*mean* age = 16 y) for their growth, health, and development.

Inclusion criteria for study participation were birthweight greater than 3 kilograms, absence of pre- or postnatal complications, and no known neurological deficits. The analytic sample for the current study is 1059 participants who completed the Achenbach Youth Self Report (YSR) of behavior questionnaire and other variables of interest.[20,21] Informed consent was provided by all participating families and ascent was provided by youth at the adolescent wave. The Institutional Review Boards of the relevant study sites approved the study and all materials.

Measures

Iron deficiency and iron deficiency anemia in infancy

Iron deficiency was assessed at 6m, 12m, and 18m and defined as 2 out of 3 iron measures within the deficient range (mean cell volume < 70 fl, erythrocyte protoporphyrin ≥ 1.77 uM red blood cells and serum ferritin < 12 ug/L). Iron deficiency anemia (IDA) was defined as venous hemoglobin ≤ 100 g/L

at 6 months and <110 g/L at 12 and 18 m. These criteria are the standard in the field.[22] Infants who were iron deficient or iron deficient anemic at any onetime point at 6-, 12-, or 18-months received a code of '1' or 'ever ID/IDA'; those who were iron sufficient received a code of '0'.

Overweight and obese weight in adolescence

Height and weight were measured while individuals were in minimal clothing and without shoes during laboratory visits using a digital scale (0.1 kg precision) and a stadiometer (0.1 cm precision) according to standardized methods. Body mass index (BMI = kg/m^2) was calculated and translated to a BMI percentile adjusting for age and sex according to CDC norms The resulting percentile was used to classify children as normal weight or overweight/obese (OW/OB; BMI ≥ 85^{th} percentile).[23]

Two-hit exposure

Two-hit exposure is defined as individuals who were exposed to a 'two-hit' nutritional insult of ID/IDA in infancy first and OW/OB in adolescence second.

Externalizing problems behavior in adolescence

Adolescent behavioral problems were assessed by youth ratings on a 76-item Youth Self-Report (YSR) instrument (Cronbach's alpha = 0.85).[20] The purpose of the questionnaire is to provide standardized description of behavioral dimensions (e.g. behaviors, feelings, thoughts, and competencies) and not to diagnose specific psychiatric disorders. Each item is scored on a 3-point scale, where 0= not true, 1=somewhat or sometimes true, and 2= very often or often true. Externalizing syndromes are derived from a composite of scores on the

aggressive, delinquent, and intrusive behavior sub-scales.[20,24] Example questions include “I destroy my own things,” “I threaten to hurt people,” and “I do not feel guilty after misbehaving.” For the externalizing behavior scales, the 90th percentile (or T-score> 60) is considered the clinical cutoff for a referral. Adolescents who scored above the 90th percentile received a code of ‘1’ while those with below or equal than 90th percentile received a code of ‘0’.

Covariates

The extent of supportive environment within the household at the time of the infant assessment was assessed by the Home Observation for Measurement of the Environment (HOME) inventory, and is used as a covariate given its known association with youths’ problem behaviors[25,26] The HOME questionnaire was administered to the mother or primary caretaker during the home visit in infancy. Other covariates include child gender, age of assessment in adolescence, and the family’s socioeconomic status as measured by the Graffar instrument at adolescence.[27]

Statistical analysis

Statistical analyses for this study were completed using the SAS Systems for Windows (version 9.3, SAS Institute, Inc, Cary, NC) and SPSS (version 21, IBM SPSS Statistics, IBM Corporation). Given general consensus in assessing the multiplicative and additive effects when the outcome is binary, we assessed two separate indices – one for multiplicativity and another for additivity. For index of multiplicativity, logistic regression was used to adjust for covariates. The bias-corrected and accelerated (BCa) bootstrap procedure was used to obtain

standard errors and confidence intervals.[28] Indices of additivity were estimated using linear binomial regression with robust estimates of variance.[29,30] The main purpose of using linear binomial regression is to estimate the partial effect of the independent variable on the outcome probability, not the predicted values of outcome within the interval (0,1). The estimated regression coefficients can be interpreted as marginal effects. Moreover, the role of infant iron deficiency status and adolescent OW/OB in predicting adolescents' externalizing problem behavior as joint or separate was evaluated by a series of indices of additive interaction, which evaluated several indices including the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and synergy index (S).[31] The relative excess risk due to interaction (RERI>1) can be interpreted as the risk that is additional to the risk that is expected on the basis of the addition of the odds ratios under exposure. The attributable proportion due to interaction (AP) can be interpreted as the proportion of behavior problems that is due to the interaction among individuals who have Two-hit exposures. The synergy index (S), can be interpreted as the excess risk from exposure to both exposures when there is interaction relative to the risk from exposure without interaction.

RESULTS

Approximately half of the sample was male (51%). Mean age at the adolescent wave assessment was 16.2 years (SD=0.5). On average, mothers completed 9 years of education (SD=2.7), and had scores below the median on

the supportive environment in infancy measure of supportive environment (HOME) and the socioeconomic scale in adolescence. (Table 1).

Table 2 summarizes results of the regression models examining the multiplicative effect adjusting for covariates. Odds ratios with confidence intervals are presented for the ID/IDA status only (OR=1.44; 95% CI= 0.91, 2.09), for OW/OB status only (OR= 1.35; 95% CI: 0.93, 1.96), and for the ID/IDA and OW/OB statuses (OR=1.67; 95% CI: 1.05, 2.69; 'two-hit'), where iron sufficient and normal weight status is the reference category. Adolescents with a 'two-hit' insult had a positive deviation from multiplicativity. In other words, we observed the presence of an interaction on a multiplicative scale between iron deficiency and weight status on externalizing problems behavior as compared to the healthy counterparts.

Indices for measuring interaction on the additive scale are presented on Table 3. All indices of additive interaction ($\beta=0.1$; $p<0.05$) including relative excess risk due to interaction (RERI=1.4), attributable proportion to the joint effect (AP=0.45 or 45%), and synergy index (S=2.9) indicate a positive direction and magnitude of an additive effect between the two exposures on externalizing problem behaviors. However, the interaction on the additive scale of the RERI is less than a threshold of 2. Thus, the additive scale cannot be concluded to be causative as defined in the sufficient cause model without the assumption of monotonicity (e.g. a causal pathway).[32]

DISCUSSION

In the present study, we demonstrated that a two-hit nutritional insult shows a positive deviation from additivity and multiplicativity on youth externalizing problem behaviors beyond having either condition alone.

Our main findings provide evidence of the joint effect of the two-hit insult that may impact youth externalizing behavioral problems. The positive deviation from multiplicativity of two exposures strengthens the expectation that being subjected to two exposures at two critical developmental periods is associated with externalizing problem behaviors. Demonstration of a multiplicative effect is important in the search for etiologic pathways associated with externalizing problems behavior. In the context of brain development of Chilean adolescents in our study, it is plausible that ID/IDA in infancy causes an initial insult to the brain, which makes the brain more susceptible to the chronic inflammation of OW/OB in adolescence, which in turn disrupts how the brain processes and responds to social information. In our previous work, we tested the two-hit insult hypothesis on cognitive functioning and found that both timing and the severity of the nutritional insult are important to brain development and function. For instance, the role that iron plays in early-life brain-circuit development[5] and the detrimental effects on stimulus-response relationship during adolescence may provide additional insight into the etiological pathways of nutritional insult to externalizing problems behavior during adolescence. As the neural capacity developed during infancy is fixed throughout the lifespan, the damage caused by iron deficiency in infancy can contribute to longer reaction times and latencies in

the ability to process and respond to environmental information and potentially enhance risk-taking behavior in adolescence.[6,33] Moreover, many epidemiological studies have reported a correlation between the OW/OB adolescents and a range of maladaptive personal traits, poorer response-inhibition, and self-control.[11,34] As adolescence marks a critical period of renewal and remediation through neural plasticity that is capable of reprogramming the effects of earlier life in ways consistent with current experience, [6,35] obesity (e.g., excess fat, inflammation, and metabolic dysfunction) in adolescence may exaceberate the issue of poor inhibitory control and disrupts both input and output in brain-behavioral manifestations.[35] Our findings indicate that behavioral problems are not necessarily due to one isolated period of insult as the organization and function of neural systems. Instead, it is established in earlier developmental periods, which in turn can shape later stages of neurobiological sensitivity and may partly reflect the influence of early social environment, especially during adolescence. Isolation and documentation of single point nutritional insult, while useful, provides only a limited understanding of the linkage between nutrition and brain-behavioral manifestations.

In addition to the multiplicative effect, our study demonstrates a positive deviation from additivity (significant product term from linear binomial regression, RERI > 1, AP=0.45, and S=2.4), which implies significant additive interaction. This demonstration of an additive effect is important as it highlights ways to better tailor nutritional interventions that address the public health significance of the Two-hit exposure.[36] The obscurity of individual physiological effects and the

role of environment involved in the Two-hit insult makes it less clear how much more concern is warranted for truly joint effects. In other words, it is unclear whether the reduction in externalizing problem behavior may be substantially ameliorated by correcting one exposure compared to addressing Two-hit exposures. As the current study indicates that the effect of the Two-hit exposure is additive, it does not implicate a syndemic. Therefore, ID/IDA and OW/OB epidemics need not be addressed jointly in order to reduce externalizing problem behavior. Rather, one could implement an intervention to reduce ID/IDA to reduce the burden of externalizing problems behavior even if another risk factor continued unabated. For example, from our two-hit insult hypothesis, which we define as occurring at infancy and adolescence, it is not apparent that an intervention that simultaneously targets iron deficiency status and OW/OB would be useful. Based on the attributable proportion of the joint effect of these two exposures, it is possible that ameliorating ID/IDA in infancy may actually have a greater preventive impact on reducing externalizing problem behaviors in adolescence than would otherwise be predicted in a model where no joint effects were observed. Furthermore, since nutritional iron deficiency and iron deficiency anemia continue to be widespread [37,38], prevention would likely improve the neurodevelopmental capacity of millions of the world's most vulnerable children during developmentally critical periods. This finding would be of substantive interest to public health practitioners faced with allocating scarce resources or feasibility across multiple sectors.

Limitation

The literature is inconclusive in terms of the monotonic effect of ID/IDA in infancy and OW/OB in adolescence and their relationship to externalizing problem behaviors. Currently, the two-hit insult hypothesis clearly lacks sufficient evidences to permit causal inference and needs further testing. Moreover, it is challenging to describe variability in behavioral dimensions that is not explained by self-reported measures. Even with the advancement in neuroimaging and neural activation research, it is difficult to predict externalizing behavior either concurrently or in the future. Further studies on the role of nutrition in brain development and its properties and mechanisms in social contexts may advance the field by yielding additional information about the conditions and mechanisms that underlie how neurobiological variability predicts engagement in health-compromising behaviors.

Conclusion

The present study highlights the importance of considering two independent epidemics for understanding the joint and additive effects for individuals' behavior in the context of brain development. Future studies have an opportunity to extend the current findings by considering the extent to which other nutritional insults – e.g., malnutrition and micronutrient deficiency – interact to impact psychosocial health and development.

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Table 4.1. Descriptive characteristic

Variable	% or mean (SD)
Clinically meaningful externalizing behavior	20.9
ID/IDA in infancy	27.2
OWOB in adolescence	35.3
Age of assessment in adolescence	16.24 (0.48)
Male	51.3
Mother's education	9.47 (2.73)
HOME-Infancy (range 12-42; median 31.00)	30.30 (4.73)
Socioeconomic status in adolescence (range 18-58)	33.33 (6.81)

Table 4.2. Impact on index of multiplicativity: odds of exhibiting externalizing behavior disorder above clinical cutoffs

Exposures	Odds ratio	BCa 95% confidence interval
ID/IDA alone	1.44	(0.94, 2.61)
OW/OB alone	1.35	(0.93, 1.96)
ID/IDA and OW/OB *	1.67	(1.06, 2.61)

*P<0.05; ORs are adjusted for age, gender, years of maternal education, supportive environment in infancy, SES in adolescence

Table 4.3. Impact on indices of additivity: betas from linear binomial regression, relative excess risk due to interaction, attributable proportion, and synergy index

Index of additivity: linear binomial regression		
Exposures	Beta	95% confidence interval
ID/IDA alone	0.06	(0.99, 1.14)
OW/OB alone	0.04	(0.98, 1.11)
ID/IDA and OW/OB*	0.10	(1.01, 1.21)
Indices of additivity: RERI, AP, and S**		
RERI (95% CI)	AP (95%CI)	S (95% CI)
1.40 (-0.73, 3.54)	0.45 (0.15, 0.74)	2.92 (1.53, 5.59)

*P< 0.05; Beta is adjusted for age, sex, years of maternal education, supportive environment in infancy, and SES in adolescence

** RERI= Relative excess risk due to interaction; AP= Proportion attributable to the interaction; S= synergy index

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CHAPTER 5: DISCUSSION

THE DUAL BURDEN OF NUTRITIONAL DISORDERS

In Chapter 2, we presented evidence of the intended and unintended consequences of economic growth and nutritional changes on children's nutritional outcomes. The trends in increasing per capita income and food availability from 1990 to 2010 in Brazil, Chile, and Mexico paralleled the decreasing trends in calorie-based undernutrition. The change in the quality of diets provided further evidence for the existence of nutritional transitions in all three selected countries, all of which underwent significant improvements in per capita availability of meat, while per capita availability of fruits and vegetables remained constant. This limited and unbalanced dietary improvement provides evidence for the coexistence of micronutrient deficiencies and overnutrition among children as indicated by the continued persistence of children with micronutrient problems and the increasing trends in childhood obesity.

The need for integrated interventions

Government policy and programs have facilitated economic environments that support the shift in secular nutrition trends by increasing food availability to all people.[1-5] In reviewing the successful policies and strategies implemented by each country to reduce the prevalence of calorie-based undernutrition, we found that political momentum, national coordination structures, and alignment of social programs with national nutritional strategies to be the most important elements in reducing the prevalence of calorie-based underweight children. For micronutrient

deficiencies, innovative and successful fortification and supplementation programs are available for each country.[6-9] In the context of Brazil, Chile, and Mexico, it is clear that all successful policy integrated and nutrition based programs to date have been interventions that targeted one-nutrient deficiency at a time.[1,4,5] However, we are not aware of equally successful strategies and elements for addressing calorie-based undernutrition or micronutrient deficiencies without adding to the burden of growing prevalence of overweight and obesity in children. Chapter 2 suggests that the development of effective integrated interventions to tackle the dual burden of micronutrient deficiency and obesity requires a robust understanding of the multifaceted nature of the disorder along with prolonged individual behavioral programming. Improved understanding of the complex, intertwined nature and broad-spectrum of nutritional disorders is important for developing national programs, improving inter-institutional coordination and creating more effective policies that are sustainable within the framework of each country's means and needs. Future policies and programs must take into account the multifaceted nature of nutrition because nutrition is about more than the absence of visible or invisible forms of nutrient deficiency or the presence of obesity. In the future, national initiatives and inter-institutional coordination will benefit from promoting healthier economic and societal development while integrating nutritionally relevant indicators in initiatives and programs.

Much work remains to be done to develop national initiatives and improve inter-institutional coordination to create policies that are more effective. Chapter 2

contributes to this effort by increasing the understanding of childhood nutritional disorders and their complexities, and offers guidance for action in the Latin American region.

THE TWO-HIT INSULT AND BRAIN-BEHAVIORAL MANIFESTATION

From a developmental perspective, the brain has sensitive periods during which exposure to nutrient deficiencies or an excess of nutrients can cause adverse effects and reduce brain functioning.[10-13] Chapters 3 and 4 of this dissertation describe one type of two-hit nutritional insult that occurred during key developmental phases in infancy and adolescence are associated with compromised brain performance and behavioral problems. A single exposure to a nutritional insult does not appear to create a significant impact when compared to participants that were not exposed to nutritional insults.

In Chapter 3, our analysis provides empirical evidence showing that overweight and obese adolescents who were iron deficient during infancy had significantly longer reaction times, almost doubling the effect compared to individuals with either iron deficiency or obesity alone. In addition, the finding suggests that two-hit insults may affect brain function negatively throughout life. The combination of poorer brain-circuit development during infancy due to infant iron deficiency[14,15] and chronic inflammation caused by adolescent overweight/ obesity[16] appears to have an additive effect and may be the cause of the slower reaction times observed. To demonstrate the proportion of individuals with slower reactions times that can be explained by joint exposure, we conducted an

additional analysis to compute the attributable proportion due to interaction.[17] The proportion attributable to joint exposure was 40%. The second largest attributable proportion came from adolescent OW/OB alone (35%), and infant ID/IDA alone accounted for 25%. The proportion implies that concomitant exposure of ID/IDA and OW/OB status escalates developmental risk and can lead to decreases in brain processing speed. Therefore, when abnormal nutritional status impacts individuals two or more times during sensitive developmental periods, the impact appears to put individuals at greater risk for poorer neurocognitive performance, including poorer brain processing speed and response inhibition.

Causal interaction between iron deficiency and weight status?

In Chapters 1, we defined causal interaction as the interaction between two risk factors, which taken together cause adverse brain-behavior manifestations as defined by a deviation from additivity of the risk difference scale of the two risk factors under study.[18,19] It should be noted that the observed joint effect in Chapter 3 and 4 does not imply an understanding of the underlying causal mechanisms. This is because the extent to which the literature supports the monotonic effect of the single-hit insult (ID/IDA or OW/OB) as a potential causal pathway that amplifies adverse brain-behavioral manifestations at the biological level remains unclear.[20]

Our findings provide empirical evidence of an additive and multiplicative impact by including a product term of the two risk factors in the statistical model. For example, in Chapter 4, the main finding is a positive deviation from

multiplicativity of two exposures (OR= 1.7; 95% CI 1.1, 2.6), which strengthens the expectation that being subjected to two exposures is associated with externalizing problem behaviors. By demonstrating the impact of a two-hit insult in multiplicative form, our findings contribute to the search for etiologic pathways for externalizing problem behaviors in adolescence. Additionally, our findings suggest that behavior problems are not necessarily due to one isolated period of insult during a key period of neural system development. Instead, damage incurred during earlier developmental periods can shape later stages of neurobiological sensitivity and may partly reflect the influence of early social environments, especially during adolescence.[13] Isolation and documentation of a single point nutritional insult, while useful, provides only limited understanding of the linkage between nutrition and brain-behavioral manifestations in the context of brain development and functioning.

Demonstration of an additive impact is especially relevant when addressing the public health impact of joint exposures. One motivation for studying additivity is to identify which exposure (e.g., ID/IDA or OW/OB) would benefit most from intervention when resources are limited.[21] In settings in which it is not possible directly intervene on the primary exposure of interest (e.g., OW/OB), one might instead be interested in which other exposure cold be changed to eliminate the effect of the adverse effect of interest. However, assessing the importance of a joint effect based on a coefficient estimate of a product term in a statistical model is limiting.[18] The estimation method we implemented in Chapter 3 provides additional information and is an easier

method for assessing the importance of an additive interaction. Our study indicates that 40% of slower reaction times were due to joint exposure, whereas ID/IDA in infancy by itself attributed about 25% of the effect. The proportion attributable to the single exposure implies that adverse neurocognitive effects can be averted by simply preventing iron deficiency in infancy. For example, in environments where a two-hit insult is common, it may not be feasible to implement an intervention that simultaneously targets ID/IDA and OW/OB because they occur at two different points in time. Based on the additive interaction and the attributable proportion of the joint effect, it is possible to quantify the effect that ameliorating iron deficiency in infancy may actually have a greater preventive impact on reducing adverse brain-behavioral manifestations in adolescence than would otherwise be predicted in a model where no joint effects were observed.

STRENGTHS AND LIMITATIONS

Generalizability

Dual burden of nutritional disorders

In Chapter 2, we used publicly available, country-level data for Brazil, Chile and Mexico. A meta regression analysis done by Jones-Smith suggests that increased per capita GDP is associated with an increase in the absolute annual change in prevalence of overweight and obesity.[22] Thus, the concept of an economic and nutrition transition applies directly or indirectly to all low-income, middle-income, and transitioning countries. The analysis provided in Chapter 2 is expected to increase understanding of the multifaceted nature of

nutrition and contribute to the effort to address the global epidemic of dual burden of nutritional disorders.

Two-hit insult

Evidence presented in Chapter 3 and 4 have limited external generalizability in the context of Latin American countries. The original preventive trial of the Santiago Longitudinal Study initiated when nutritional iron deficiency and iron deficiency anemia was common in Santiago, Chile; however, it is important to note the policy that the Chilean government reinforced in mid 90s.[1,23] One of the policies required clinics to distribute iron supplementation to infants, which caused an unanticipated change in the study design. Although the impact of the preventive trial of iron deficiency anemia in infancy is not significantly affected by it, the iron deficiency level in the cohort we studied raged from mild to moderate. Therefore, two-hit insult findings and brain-behavioral manifestations may not be generalizable to populations with a chronic and severe iron deficiency anemia status in some low- to middle-income countries such as Guatemala.

On the other hand, our study has strong internal validity. Using 2 of 3 abnormal iron measures to define iron deficiency and iron deficiency anemia, the study clearly captures the participants' iron status in infancy. All the anthropometric measurements were assessed with the highest protocol standards for all measurements at the Nutrition Research Center at the University of Chile.

Statistical power and measurement

The findings reported in Chapter 3 were drawn from a small subset of 116 participants who completed a computerized neurocognitive assessment. The sample group for our study on neurocognitive functioning was sufficient for detecting small effects. Larger sample sizes of adolescents with computerized neurocognitive assessments are needed to confirm our findings and to provide more precise estimates of the relationship between two-hit insult and neurocognitive functioning and performances.

Chapter 4 used Achenbach's Youth Self-Report instrument. The purpose of the questionnaire was to provide a standardized description of behavioral dimensions and not to diagnose specific psychiatric disorders. It is challenging to describe variability in behavior that is not explained by self-reported measures. Even with the advancement of neuroimaging and neural activation research, predicting behavior either concurrently or in the future remains difficult.[24]

RECOMMENDATIONS AND FUTURE RESEARCH NEEDS

Dual burden of nutritional disorders

In Chapter 2, we emphasized the intertwined role of nutrition as explicitly presented in the post-2015 Sustainable Development Goals (SDGs). Nutrition plays a large role in these synergistic and mutually supportive goals as both a cause and an outcome of the SDGs as a whole.[25,26] With cases of successful policy integration and nutrition-based programs in Brazil, Chile, and Mexico, it is important for Latin American countries to promote healthier economic

development while integrating nutritional indicators in each initiative and project. Future national initiatives and inter-institutional coordination will benefit from promoting healthier economic and societal development while integrating nutrition-relevant indicators in each initiative and project.[5]

Two-hit insult

Our study contributes to the existing literature by presenting empirical evidence that nutritional insults that occur during two developmentally sensitive periods have an additive and multiplicative effect, but not a causal effect on neurocognitive performance and externalizing problem behaviors. More research is needed to better understand the directionality and magnitude of the association between ‘two-hit’ or ‘multiple-hit’ nutritional insults and individual brain functioning.

Understanding the adverse outcomes of two-hit nutritional insult during key developmental periods is imperative to designing effective interventions aimed at mitigating adverse effects on brain development and performance. Given the consequences of developmental delays in neurocognitive functioning and adverse behavioral manifestations, strategies to prevent iron deficiency and iron deficiency anemia during infancy and programs that promote neural plasticity in later years warrant more attention.

CONCLUSIONS

It is clear that nutritional status, diet, and the ingestion of a range of nutrients impact neurocognitive development, function, and performance. This dissertation

study provides evidence that the dual burden of nutritional disorders and two-hit insult concepts have proved useful in understanding the co-existence of micronutrient deficiencies and obesity and the impact of the additive effect of two different nutritional insults on cognitive development and functioning.

The study provides empirical evidence that exposure to ID/IDA in infancy and OW/OB in adolescence is significantly associated with slower neurocognitive performance, while OW/OB or ID/IDA alone did not significantly alter neurocognitive performance. Evidence also indicates that ID/IDA during infancy has a generalized impact on brain development, which increases the risk for long-term cognitive impairment. We suggest that exposures to OW/OB and ID/IDA during sensitive developmental periods may act additively to disrupt the timing of key steps in brain development and derail the normal progression of neuro-functional maturation. Taken together, the evidence suggests that adequate nutrition during important developmental periods, including prenatal, infancy, childhood, and including adulthood is important for optimal brain development and performance.

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