BIRTH SIZE, INFANT GROWTH, AND CHILD BMI AT AGE
5 YEARS IN A MULTIETHNIC POPULATION

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAI‘I AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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ABSTRACT

Child overweight is a public health concern and it is imperative that steps are taken to examine early factors that may contribute to this unhealthful start to life. Prenatal and postnatal determinants of overweight (e.g., maternal overweight, birth weight, and increased weight gain during infancy) have been studied. However, few studies have examined the effect of other measures of birth size (birth length, indices of weight/length, gestational age) and infant growth patterns on BMI at age five years in a multiethnic population.

This is a retrospective, longitudinal study using data from the Kaiser Permanente Hawai‘i Electronic Medical Record. Singleton children, born in years 2004 and 2005 at Kaiser Permanente, with birth and linked maternal information were initially included (n = 894). Subsequently, children with measured weights (n = 597) and lengths (n = 473) from ages 2 to 4 and 22 to 24 months were included.

A higher birth weight was associated with a higher BMI at age five years after controlling for gestational age, age, sex, race/ethnicity, and maternal factors (pre-pregnancy weight, age, education, and smoking). Birth length was not associated with BMI at age five after adjusting for birth weight and gestational age. A higher pre-pregnancy maternal weight was also associated with a higher child BMI at age five years.

For every 100 g/month increase in weight and 1 cm increase in length over the infant period of 20 months, BMI increased by 1 kg/m² at age five years. However, this was not true for change in BMI during infancy. The effect of birth weight on BMI at age five years was not mediated by infant growth and the interaction was not significant.
Birth weight, change in infant weight, and BMI at age five varied by race/ethnicity, but not by sex. Birth weight and change in infant weight was higher in Whites and Other Pacific Islanders, with most differences observed after age two years.

Early indicators such as a higher birth weight and change in infant weight and length, and higher maternal pre-pregnancy weight, are key indicators associated with a higher child BMI at age five.
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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>AAP</td>
<td>American Academy of Pediatrics</td>
</tr>
<tr>
<td>AFRI</td>
<td>Agriculture and Food Research Initiative</td>
</tr>
<tr>
<td>AGA</td>
<td>Appropriate-for Gestational Age</td>
</tr>
<tr>
<td>ALSPAC</td>
<td>Avon Longitudinal Study of Parents and Children</td>
</tr>
<tr>
<td>AC</td>
<td>Abdominal Circumference</td>
</tr>
<tr>
<td>AR</td>
<td>Adiposity Rebound</td>
</tr>
<tr>
<td>BIV</td>
<td>Biologically Implausible Values</td>
</tr>
<tr>
<td>BIVWT</td>
<td>Biologically Implausible Values for Weight</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>BPL</td>
<td>Biparietal Diameter</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
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<tr>
<td>EMR</td>
<td>Electronic Medical Records</td>
</tr>
<tr>
<td>FITS</td>
<td>Feeding Infants and Toddlers Study</td>
</tr>
<tr>
<td>FL</td>
<td>Femur Length</td>
</tr>
<tr>
<td>GDM</td>
<td>Gestational Diabetes Mellitus</td>
</tr>
<tr>
<td>GWG</td>
<td>Gestational Weight Gain</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Insulin Like Growth Factor-1</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine Growth Retardation</td>
</tr>
<tr>
<td>IOM</td>
<td>Institute of Medicine</td>
</tr>
<tr>
<td>IOTF</td>
<td>International Obesity Task Force</td>
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<tr>
<td>KPH</td>
<td>Kaiser Permanente Hawai‘i</td>
</tr>
<tr>
<td>LGA</td>
<td>Large-for-Gestational Age</td>
</tr>
<tr>
<td>LMP</td>
<td>Last Menstrual Period</td>
</tr>
<tr>
<td>HC</td>
<td>Head Circumference</td>
</tr>
<tr>
<td>HMO</td>
<td>Health Maintenance Organization</td>
</tr>
<tr>
<td>HMORN</td>
<td>Health Maintenance Organization Research Network</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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</tr>
<tr>
<td>MRN</td>
<td>Medical Record Number</td>
</tr>
<tr>
<td>NCHS</td>
<td>National Center for Health Statistics</td>
</tr>
<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>NIFA</td>
<td>National Institute of Food and Agriculture</td>
</tr>
<tr>
<td>NOS</td>
<td>None Other Specified</td>
</tr>
<tr>
<td>NRI</td>
<td>National Research Initiative</td>
</tr>
<tr>
<td>OB</td>
<td>Obstetrics</td>
</tr>
<tr>
<td>OB/GYN</td>
<td>Obstetrics and Gynecology</td>
</tr>
<tr>
<td>OMB</td>
<td>Office of Management and Budget</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PacDASH</td>
<td>Pacific Kids DASH for Health</td>
</tr>
<tr>
<td>PCP</td>
<td>Primary Care Physician</td>
</tr>
<tr>
<td>PI</td>
<td>Pacific Islander</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Curve</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance Epidemiology and End Results</td>
</tr>
<tr>
<td>SES</td>
<td>Socioeconomic Status</td>
</tr>
<tr>
<td>SGA</td>
<td>Small-for-Gestational Age</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
<tr>
<td>USDA</td>
<td>United States Department of Agriculture</td>
</tr>
<tr>
<td>VDW</td>
<td>Virtual Data Warehouse</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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CHAPTER 1. INTRODUCTION

1.1 Child Overweight

Child overweight is a public health concern. The prevalence of childhood overweight has more than doubled among younger children and tripled for adolescents in the contiguous United States (US) since 1980. According to the recent National Health and Nutrition Examination Survey (NHANES) 2007 – 2008, 31.7% and 16.9% of US children and adolescents ages 2 to 19 years had a Body Mass Index (BMI)-for-age > 85th and > 95th percentile respectively (percentiles based on 1963 – 1994 data). Prevalence of obesity in 8,550 four year old children born in the US was reported at 18.4% in 2005 among American Indian/Native Alaskan, Hispanic, non-Hispanic Black, non-Hispanic White, and Asian ethnic groups. In the state of Hawai‘i, a study conducted on 10,199 public school students entering kindergarten (ages 4 to 6, completed in 2002 – 2003), found a prevalence of 28.5% overweight and obese.

Child overweight varies by ethnicity, starting as early as four years of age where the distribution of obese children within ethnic groups (n = 8,550) was reported as Native American (31%), Hispanic (22%), African American (21%), White (16%), and Asian (13%). NHANES reported that African American and Mexican American children (ages 6 to 11) were more likely to be overweight than non-Hispanic, White children. Baruffi et al. reported that, within a cross-sectional study of 21,911 children participating in the Hawai‘i Special Supplemental Nutrition Program for Women, Infants, and Children (1997-1998), Samoan children were heaviest (n = 633, 27.0% obese, ≥ 95th percentile) and Asians the least heavy (n = 630, 12.2% underweight, < 10th percentile) among 2 to 4 year olds. Racial/ethnic disparities in early life risk factors for child obesity are present in the infant and preschool years. African American and Hispanic children grew rapidly in the first six months and were more likely to consume sugar sweetened beverages and fast foods after two years of age in comparison with White children.

Common co-morbidity disorders in overweight children include elevated blood pressure, elevated cholesterol, triglyceride, and insulin levels, and psychosocial problems. In addition, child overweight increases later risk for morbidity even if it may not persist in adulthood. Child overweight is also shown to track strongly into
adolescence and adulthood.\textsuperscript{10,11} In a study with 233 children, excess weight gain in the primary school-aged child was gained by age five years; and, weight at age five years predicted weight at age nine years.\textsuperscript{12} BMI at a younger age was correlated with later adult BMI.\textsuperscript{13,14} Increased BMI z-scores at age 21 years were observed for children who were normal weight at age five years and at Tanner pubertal stage four or five for breast/genitalia and pubic hair development at age 14 years.\textsuperscript{13} In comparison, overweight children at age five years had an even greater increase in BMI z-scores at age 21 years regardless of the stage of puberty at age 14 years.

Other literature has demonstrated that child overweight is associated with early onset of puberty and early age at menarche,\textsuperscript{15} which are predictive of subsequent risk of obesity,\textsuperscript{16} insulin resistance,\textsuperscript{17} and breast cancer later in life.\textsuperscript{18} Hormone-dependent cancers such as breast cancer are associated with early age at menarche due to much earlier and longer estrogen exposure over time.\textsuperscript{19-21} A possible mechanism includes the role of rapid growth during infancy resulting in taller childhood stature, early induction of growth hormone receptors, and thus high levels of insulin-like growth factor-1 (IGF-1).\textsuperscript{22} Higher levels of IGF-1 are positively associated with breast and prostate cancer.\textsuperscript{23} Small size at birth and rapid growth from 0 to 2 years was associated with early puberty.\textsuperscript{15} More specifically, rapid weight gain was associated with child obesity at ages 5 and 8 years, with evidence for insulin resistance as determined by high fasting insulin. In addition, earlier onset of adrenarche as measured by early androgen secretion and low levels of sex hormone-binding globulin decreasing the body’s ability to regulate sex steroid bioavailability\textsuperscript{22} were also observed.

Early infant weight gain in the first six months was associated with increased fat mass and central fat distribution in children and adolescents ages 4 to 20 years.\textsuperscript{24} Weight gain in the first two years of life was associated with more peripheral fat distribution.\textsuperscript{25} These findings suggest that prevention should begin in early infancy and childhood to deter metabolic changes that would result in an altered trajectory towards obesity later in life.
1.1.1 Definitions and Identification of Child Overweight

Within the child overweight literature, definitions of child ‘overweight’ and ‘obesity’ vary across studies, between countries, and over time. Most of these definitions describe body weight or weight adjusted for height as opposed to fatness.26

The Centers for Disease Control and Prevention (CDC) and American Academy of Pediatrics (AAP) recommend use of BMI-for-sex and age-specific percentiles for overweight and obesity screening in children and teens ages, 2 to 19 years. BMI is plotted to obtain a percentile ranking, which is used as an indicator of size and growth of individual children, and is compared to children of the same sex and age. Table 1.1 shows the current CDC-defined BMI weight status categories for percentile ranking used with children and teens.27

It is important to note that according to CDC, BMI is a screening tool, not a diagnostic tool.27 BMI values are useful for screening and population surveillance;

<table>
<thead>
<tr>
<th>Weight Status Category</th>
<th>Percentile Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 5th percentile</td>
</tr>
<tr>
<td>Healthy Weight</td>
<td>5&lt;sup&gt;th&lt;/sup&gt; percentile - &lt; 85&lt;sup&gt;th&lt;/sup&gt; percentile</td>
</tr>
<tr>
<td>Overweight</td>
<td>85&lt;sup&gt;th&lt;/sup&gt; percentile - &lt; 95&lt;sup&gt;th&lt;/sup&gt; percentile</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 95&lt;sup&gt;th&lt;/sup&gt; percentile</td>
</tr>
</tbody>
</table>

however, they do not identify children who are at risk for excess fat or for future weight and health related problems on an individual basis. The Childhood Obesity Task Force of the United States Preventive Services Task Force28 stated that more studies are needed to determine what might be the best indicator for children at risk for future health outcomes due to overweight or obesity. For the purposes of this study, ‘child overweight’ will be used as an overall term to reflect the biological status of children in relation to either overweight or obesity.
1.1.2 Determinants of Child Overweight

Multiple factors are related to the development of child obesity. Genetics, imbalance of energy intake and expenditure, culture, and the ‘obesogenic’ environment are a few known factors that contribute to the obese state.29 Development of child obesity has also been discussed as having origins in utero with a continuous influence on later periods of growth and development. Figure 1.1 illustrates potential risk factors for child overweight during pregnancy, birth and infancy. Furthermore, subsequent risk for early expression of disease during adolescence and adulthood is exemplified.

1.2 Birth Size and Child Overweight

Birth size, a marker of conditions during pregnancy, has been found to be associated with child overweight.30 Most studies investigate birth weight, which is a measure of mass and therefore a starting point for weight gain and part of the BMI. Birth length, on the contrary, has not been examined in relation to child overweight, although it is part of the BMI measure. Measures of birth weight-for-length, often mentioned as BMI = f(weight/length^2) or ponderal index = f(weight/length^3), are examined with child and adolescent overweight.31, 32 Newborn BMI predicted child overweight at age five years.33 New World Health Organization (WHO) charts now allow for measurement of newborn BMI, whereas CDC charts only provide BMI from two years of age.34

Early literature on birth size and child obesity centered on the ‘developmental origins of adult disease’.35 Barker hypothesized that small size at birth is associated with fetal malnutrition which resulted in fetal adaption and programming to survive in a postnatal external environment of abundance thus increasing the risk for adult disease. These findings have been replicated in other studies.35-38 However, birth size has also been shown to be positively associated with child overweight.39

A most recent systematic review of birth weight and later overweight included 33 studies of 478 citations from five electronic databases.39 Thirteen studies did not provide enough dichotomous data for birth weight and obesity,11, 32, 40-50 therefore they were not included in the meta-analysis. Twenty studies were included in the meta-analysis which reported a positive relationship with birth weight and child overweight.51-71 Children
Figure 1.1. Conceptual Framework of Early Life Factors, Child Overweight, and Subsequent Disease Risk
with higher birth weights (> 4,000 g) had a two-fold higher risk (Odds Ratio (OR) = 2.07, 95% Confidence Interval (CI): 1.91 – 2.24) than those < 4,000 g. Initial analysis of low
birth weight (< 2,500 g) children reported a decreased risk of overweight compared to
children ≥ 2,500 g; however, after removal of two studies for selection bias, the
association was not significant. Sensitivity analyses determined that the lack of a low
birth weight and obesity relationship could be explained by differences in study design,
sample size, and quality of studies. Sensitivity analyses determined that the lack of a low
birth weight and obesity relationship could be explained by differences in study design,
sample size, and quality of studies. Other studies suggest that low birth weight results
in later rapid growth and future obesity. In the systematic review, the authors also
performed subgroup analysis with different growth and developmental stages of children
and adolescents. High birth weight remained positively associated with increased risk of
obesity. They concluded that birth weight may play a role as a mediator between prenatal
status and later obesity risk. Limitations to the meta-analysis included differences in
study methods such as methodology for capturing birth weight information as
measurements vs. questionnaires and interviews administered at different postnatal ages.
Also, obesity was determined using different definitions, both reported and measured.
Lastly, seventy percent of studies included in the meta-analysis were done in China.

Previous literature examined BMI attained in childhood and adulthood; most
studies cited a positive relationship with birth weight. Reported BMI magnitude ranges
were 0.5 to 0.7 kg/m² for each 1 kg increment in birth weight. However, there were a few limitations to these studies, including lack of adequate data on gestational age, birth length, parental body size, maternal tobacco use, and socioeconomic status. In addition, some of the studies were published at a time when few premature babies survived into adulthood compared with current survival rates. Adjustment for
gestational age is critical in order to separate the effects of prematurity and impaired fetal
growth. After adjustment for gestational age, ponderal index, or birth length, few
studies have shown that the positive birth weight and child overweight relationship
remained. Other studies determined that the positive relationship of birth weight with
child overweight may be explained by accelerated growth during infancy.
1.3 Birth Size and Infant Growth

In a study of determinants of growth during early infancy, birth weight, sex, maternal smoking habits, and energy intake at four months were the main determinants of weight gain velocity (F-value >10% significance, $R^2 = 0.24$). Using stepwise regression, birth weight was inversely related to weight velocity ($r = -0.23$, $p = 0.002$), though neither birth length nor gestational age improved the model ($p = 0.10$) in the stepwise process. Gestational age was positively correlated with birth weight ($r = 0.33$) but not with weight velocity ($r = -0.05$).

1.3.1 Implications of Birth Size and Subsequent Catch-Up Growth

Previous literature led to formulation of hypotheses related to early fetal programming of size at birth, and compensatory accelerated weight velocity resulting in overweight during childhood. The most referred-to example is the recognized “natural process” of “catch-up-growth” that occurs in children who were growth-restricted in utero or small-for-gestational age. Birth weight is often viewed as a surrogate for inadequate fetal nutrition during pregnancy and is inversely associated with adult chronic disease risk. The risk is increased when considering current body size. Low-birth-weight infants experience the most postnatal catch-up growth in the first 6 to 12 months, as defined by weight or length. In a study done in the Philippines, infants in the lowest tertile for birth weight also experienced larger weight gain increments in the first six months compared with those in the middle and highest tertiles for birth weight. However, the authors do not appear to have adjusted for gestational age.

Birth weight is usually a function of gestational age and therefore gestational age should be taken into consideration due to varying lengths of gestation. Previous literature has examined the effect of birth size in terms of small- and large-for-gestational age as defined by birth weight-for-gestational age. Shorter gestation was associated with being in the tertile of fastest growth rate during birth to three months and 3 to 12 months. Rapid growth has also been observed for children whose weights are appropriate-for-gestational-age (AGA). Over a quarter of the AGA children (29%) in a German longitudinal cohort experienced rapid growth between birth and 24 months. Cameron et al. examined the relationship of rapid weight gain, obesity, and skeletal
maturity in African American children. AGA children who experienced rapid weight gain were taller and heavier and were subcutaneously fatter through childhood, independent of advanced skeletal maturity as assessed by bone age at age nine years. Cameron et al. emphasized that rapid weight gain in this sample of AGA children is not a result of regression to the mean, because anthropometric values would be expected to be closer to the 50th percentile compared to those reported for the usual gain group. Mean weight, height, and body composition values were closer to the 75th percentile for the children who experienced rapid weight gain in infancy. Maternal height was similar between normal and rapid weight gain groups, indicating that greater size in AGA children may not be genetically determined. A hypothesis for why we might see larger size and greater infant weight gain in AGA children is that they may have normal to lower birth weights or shorter gestational age.

1.3.2 Birth Length/BMI and Infant Growth

Few studies have looked at the effect of either birth length or BMI on rapid infant growth. Ong et al. examined influence of birth length on change in weight-for-age z-score greater than 0.67 Standard Deviation (SD) from birth to 24 months. The 0.67 SD is derived from the difference between centile lines on United Kingdom (UK) infant and child growth charts. A gain of > +0.67 is interpreted as “upward centile crossing” of at least one centile band (e.g., 2nd to 9th centile or 9th to 25th centile). This upward crossing of major percentile lines on UK growth infant and child growth charts is demonstrated by at least 25% of normal infants. Children with lower birth weight, length, and ponderal index values showed rapid weight-for-age gain (adjusted for gestational age) between 0 and 2 years compared with other children. In a longitudinal birth cohort (birth to age 21 years) conducted in Cebu, the Philippines, lower BMI at birth influenced rapid early infant weight gain, but not length. More work is needed to disentangle the relative role of birth weight, gestational age, and birth length in predicting rapid weight gain and eventual childhood overweight.

Early growth patterns, such as rapid growth during infancy and early ‘adiposity rebound’ in childhood, are postulated as the link amongst the relationship of fetal growth, birth size, and adult disease risk. A recent study by Singhal and
Lucas found that accelerated infant growth patterns, independent of birth size, may help to explain early ‘origins’ of cardiovascular disease.80

1.4 Early Patterns of Growth: Rapid Growth during Infancy

Rapid growth - in particular rapid weight gain - continues to be studied as a potential risk factor for subsequent obesity. A literature search began in June 2008 to obtain all available published articles on rapid growth and child overweight. PubMed was the primary search engine, and Medical Subject Headings (MeSH) of the National Library of Medicine was used to perform the literature search. MeSH key words included: “Growth and Development”, “Infant”, and “Obesity”, and limited to categories of “English”, “Human”, and “Infant: Birth to 23 months”. Articles that were referenced in citations of these papers were selected based on similar criteria. The literature search resulted in about 2060 articles between 1970 - 2012. Further restriction to categories of “gain in weight”, ‘length”, or “weight-for-length” resulted in 509 articles related to infant weight gain, 70 for infant length gain, and 18 for infant weight-for-length/height gain.

Among these articles were three systematic reviews that summarized literature examining the relationship of rapid infant weight gain and later obesity risk between 1965 and 2006.98-100 In this systematic review, Monteiro and Victoria reported that 13 of 15 articles on early rapid growth found significant positive associations with later obesity in childhood and adulthood.98 This association was independent of varying definitions of rapid growth and obesity risk or age at which rapid growth, overweight, obesity, or adiposity were measured. However, most rapid growth was assessed prior to two years of age. Studies defined rapid growth as either continuous (e.g., gain in gram weight) or dichotomous variables (e.g., > 0.67 SD). Overweight and obesity outcomes were also defined as either a continuous value (calculated BMI) or dichotomous (BMI percentile > 85th). Age range at final weight or adiposity measurement also varied from 3 to 70 years of age. Ten studies evaluated the study outcome within the first two decades of life, and methodological issues with studies included lack of representation of the original sample,50, 70, 101-104 technological limitations on statistical analysis such as computer analysis programs,94, 102, 105 not adjusting for confounders,50, 83, 94, 101, 104, 106 and inadequately addressing loss to follow-up.83, 94, 103, 105
The second systematic review evaluated 10 studies that examined the relationship of infant growth and subsequent obesity (six overlap with the previous review, plus four new studies). Seven of the 10 studies reported that rapid weight gain in infancy was associated with greater risk of obesity at ages ranging from 4.5 – 20.0 years. Six studies reported the outcome of overweight or obesity in children. In four of these studies the OR for obesity in children ranged from 1.06 – 5.70, for those who grew more rapidly in infancy compared with those who grew less rapidly. Although birth weight was controlled for in two of the four studies, gestational age was not considered. Six of seven studies adjusted for important confounders. Two studies in children failed to show an association between infant weight gain and obesity.

A review of the literature was completed by Ong and Loos (2006) to update the previous reviews and standardize the results. Only infancy weight gain up to two years and later obesity risk was assessed. Eight of the 21 studies reviewed by Ong and Loos were not included in the two previous reviews. Standardization of rapid weight gain measures has been recommended by Monteiro and Victoria who suggested use of 0.67 z-score variation for rapid weight gain. Effect sizes were transformed to a standard exposure of > +0.67 change in weight-for-age z-score to define rapid infancy weight gain. The summary of 21 studies supports a significant positive association (OR for obesity per 0.67 SD wt gain = 1.84) between rapid infancy weight gain and increased subsequent obesity risk. The earliest age of obesity assessment was at age three years; still, further analysis of datasets to examine the association of rapid weight gain during infancy and the role of birth size with child obesity is needed, since the onset of obesity continues to occur at an increasingly earlier age.

Further limitations were placed on literature collected from these early systematic reviews and on studies from 2006 to present that examine the relationship of early growth patterns and the onset of obesity at an earlier age. These limitations include: 1) that the BMI outcome was measured < 10 years of age 2) English language, and 3) measured rapid weight gain or rapid length gain or rapid weight-for-length gain, and 4) adequate consideration for methods to eliminate bias, including statistical adjustment for confounders (birth weight and gestational age). Two of the 21 studies from the three systematic reviews met these requirements. In addition, another PubMed search from
2006 to 2012 was conducted with the same key words and limits as described earlier. Three studies after 2006 did not adjust for birth weight and gestational age. Tables 1.2 – 1.5 summarize a total of eight key salient papers that met these criteria. Most studies measured weight gain, two from the three systematic reviews and three new studies. The main outcome measures were BMI z-score or category based on BMI (CDC or International Obesity Task Force (IOTF) with ages ranging from 4 to 7 years. Most studies were longitudinal in design, except for one cross-sectional study. Most studies examined were conducted in White populations (6 of 8 studies). Two studies measured change in length, one examined weight-for-length, and one change in infant BMI.

Change in weight was measured either as a continuous variable (gram weight gain per month or in a year), as a categorical variable, or as a change in weight z-score >+0.67 SD and measured in different time periods during the first two years of life in five studies. The BMI outcome was measured at different ages and was mostly defined as a categorical variable using the IOTF or CDC categories for overweight and obesity cut points. In addition use of z-scores indicates use of a reference population in the calculation, which varied among studies. The overall direction indicated by these studies (Table 1.2) is positive, indicative of a higher risk of child overweight with rapid weight gain after adjustment for potential confounders, such as birth weight and gestational age.

Different periods of rapid weight gain between birth and 24 months have been found influential on subsequent obesity. In a prospective cohort of 6,075 Chinese children, a positive association was observed between infant weight gain and child obesity, with a stronger effect for weight gain in the period of birth to three months \( \beta=0.50 \) (0.46 – 0.53) compared with weight gain during 3 to 12 months \( \beta=0.33 \) (0.28 – 0.37). Botton et al. noted two critical time periods, from birth up to six months and from two years on, in which rapid weight gain was associated with later adolescent body composition. The relationship of growth during these two time periods with later obesity is described as being controlled by different mechanisms. In the first period, growth is finally free from maternal intrauterine constraint, in which case genetics may be expressed. Weight growth is also consistently associated with later body composition. The second period is the adiposity rebound period, where fat gain
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Exposure</th>
<th>Duration: Birth to (mo/y)</th>
<th>Outcome</th>
<th>Results</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stettler (2002)</td>
<td>C</td>
<td>Weight gain in the first year of life (kg) (retrospective data, continuous)</td>
<td>1 y</td>
<td>BMI at 4.5 y (Categorical, Overwt or obesity, IOTF)</td>
<td>OR = 1.46 (1.27 - 1.67) overwt OR = 1.59 (1.29 - 1.97) obesity</td>
<td>Age, Sex, <strong>birth weight, gestational age</strong> Grade Level, Maternal BMI, Parent Occupation</td>
</tr>
<tr>
<td>Stettler, (2002)</td>
<td>PC</td>
<td>Weight gain in first four months of life (continuous, 100g/month)</td>
<td>4 mo</td>
<td>BMI at 7 y (Categorical, BMI &gt;95th percentile)</td>
<td>UnAdj OR = 1.29 (1.25-1.33) Adj OR = 1.17 (1.11 - 1.24)</td>
<td>Sex, Race, <strong>birth weight, gestational age</strong>, Weight at age 1 year (100g), First-born status, Maternal BMI, Maternal Education, Age, Study site</td>
</tr>
<tr>
<td>Karaolis-Danckert, (2006)</td>
<td>PC</td>
<td>Δ in weight z-score &gt; +0.67 SD (categorical)</td>
<td>2 y</td>
<td>BMI z-score at 7 y (Categorical, Overwt, IOTF)</td>
<td>UnAdj OR = 3.9 (1.8 - 8.3) Adj OR = 6.2 (2.4 - 16.5)</td>
<td>Sex, <strong>BMI at birth, gestational age group</strong>, Breastfeeding for 4mo, Maternal weight status and Maternal education</td>
</tr>
<tr>
<td>Dubois (2006)</td>
<td>PC</td>
<td>Ratio of the weights at both ages divided by number of months between them (categorical)</td>
<td>6 mo</td>
<td>BMI at 4.5 y (Categorical, BMI &gt;95th percentile)</td>
<td>Quintile 4 = OR 1.8 (1.0 - 3.5) Quintile 5 = OR 3.9 (1.9 - 7.9)</td>
<td><strong>Birth weight, Gestational Age</strong></td>
</tr>
</tbody>
</table>

*aPC = Prospective Cohort, C = Cross-Sectional*  
*bAA = African American"
Table 1.2. (Continued) Change in Infant Weight and Child Overweight, Adjusted for Gestational Age and Birth Weight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Exposure</th>
<th>Duration: Birth to (mo/y)</th>
<th>Outcome</th>
<th>Results</th>
<th>Covariates&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hui (2008)&lt;sup&gt;93&lt;/sup&gt;</td>
<td>PC</td>
<td>Δ in weight z-score &gt; +0.67 SD (Categorical)</td>
<td>3 mo</td>
<td>BMI z-score at 7 y (Continuous)</td>
<td>0 to 3mo $\beta = 0.50$ (0.46 - 0.53) 3 to 12 mo $\beta = 0.33$ (0.28 - 0.37)</td>
<td>Sex, Birth weight, Gestational age, BF (ever or never), Birth Order (first born or otherwise), Social Deprivation of Household</td>
</tr>
<tr>
<td>Asian M, F n = 6,075</td>
<td></td>
<td>3 mo to 1y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>PC= Prospective Cohort
Table 1.3. Change in Infant Length and Child Overweight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study$^a$</th>
<th>Exposure</th>
<th>Duration: Birth to (mo/y)</th>
<th>Outcome</th>
<th>Results</th>
<th>Covariates</th>
</tr>
</thead>
</table>
| Jones-Smith (2007)$^{31}$ Mexican M, F n = 163 | PC               | Change in length for age z-score (Continuous) | 1 y                       | BMI z-score at 4 to 6 y (Continuous) (Categorical, Overweight > 85$^{th}$ percentile) | Birth LAZ = -1 to 0
UNADJ: $\beta = 0.54$ (0.05 – 1.02)
ADJ: $\beta = 0.87$ (0.35 – 1.39)
UNADJ OR: 1.26 (0.78 - 2.03)
ADJ OR: 1.38 (0.80 - 2.39) | Gestational age, current child age, child sex, current maternal BMI, maternal height, maternal age, family SES |
| Taveras (2009)$^{113}$ White M, F n = 559     | PC               | Change in length for age z-score (Continuous) | 6 mo                      | BMI z scores at 3 y (Continuous)             | No association with BMI z-scores at 3 y                                                      | Age, gender, maternal age education, income, parity, child’s race/ethnicity, gestational weight gain, maternal smoking, maternal prepregnancy BMI, and paternal BMI |

$^a$PC = Prospective Cohort
### Table 1.4. Change in Infant Weight-for-Length and Child Overweight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Exposure</th>
<th>Duration: Birth to (mo/y)</th>
<th>Outcome</th>
<th>Results</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taveras (2009) 113 White, M, F n = 559</td>
<td>PC</td>
<td>Weight-for-length for age z-score</td>
<td>6 mo</td>
<td>BMI z scores at 3 y</td>
<td>$\beta = 0.47 \ (0.40 - 0.53)$</td>
<td>See Table 1.3</td>
</tr>
</tbody>
</table>

*PC = Prospective Cohort

### Table 1.5. Change in Infant BMI and Child Overweight

<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Study</th>
<th>Exposure</th>
<th>Duration: Birth to (mo/y)</th>
<th>Outcome</th>
<th>Results</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karaolis-Danckert (2008) 116 White, M, F n = 370</td>
<td>PC</td>
<td>BMI z-score</td>
<td>6 mo</td>
<td>BMI z-scores at 2 y</td>
<td>UNADJ: $\beta = 0.91 \pm 0.10$ p = 0.0003 ADJ: $\beta = 1.07 \pm 0.13$ p = 0.0004</td>
<td>BMI SD score at birth, gestational age group, time, bottle-feeding</td>
</tr>
</tbody>
</table>

*PC = Prospective Cohort
can explain the variability in weight gain differences in growth from age 3 to 5 years old. Postnatal weight gain, especially after two years, was an important contributor to obesity at age five years compared with birth weight and prenatal factors, such as gestational weight gain, diabetes, preeclampsia, pre-pregnancy maternal BMI, and smoking during pregnancy.119

Most rapid growth studies examined weight gain as indicator of a positive energy balance.120 Change in weight can be further described by an increase in length-for-age and weight-for-length. Change in length was measured in two studies (Table 1.3).31,113 Rapid change in length-for-age z-score from birth to age one year was not associated with increased odds of overweight in children31 and did not modify the positive relationship of length-for-age z-score at birth with odds of childhood overweight. In another study, change in length-for-age z-score was not associated with BMI z-score at age three years.113

Height or length, in addition to weight measures, provides a closer indicator of proportionality or size as well as adiposity, 121 113 and is thus a more descriptive estimate of obesity risk. One study described growth, as gain in weight, as a function of length and examined its relationship with obesity during early childhood (Table 1.4). In a study by Tavares et al., rapid increases in weight-for-length in first 6 months were positively associated with obesity at three years of age (n = 559, B = 0.51 (95% CI: 0.43 - 0.59). BMI at birth, a measure of body mass, can now be compared with international standards. Thus, it is suggested that BMI should be used to track child BMI from birth to age five years.122 Larger BMI at birth was protective OR = 0.54 (95% CI: 0.38 - 0.77) in preventing rapid weight gain (Table 1.5).116

1.5 The Role of Birth Size on Accelerated Infant Growth and Child Overweight

Early systematic reviews98, 100 did not specifically test the effect of birth size on the association of infant weight gain and child overweight. Only one study70 tested this relationship, among children presenting with intrauterine growth retardation (IUGR); however, the interaction between infants born with IUGR and infant weight gain was not significant for overweight and obesity. Two later studies demonstrated that size at birth, specifically birth weight and BMI at birth, modified the association between
rapid weight gain and child overweight. In a birth cohort of 6,075 Chinese children, lower birth weight and gestational age both contributed to faster infant weight gain from birth to three months (p<0.001) and from 3 to 12 months in boys and girls than higher birth weight and gestational age. The association of infant weight gain from birth to three months with BMI at age seven years varied by birth weight, but not with BMI between 3 and 12 months. A higher birth weight resulted in faster growth and the highest BMI z-score at age seven years compared with lower birth weights; however, the sample size for this observation was smaller due to fast growth, more commonly noted in children born with low birth weight. Between 3 and 12 months, differences in growth were only related to the effect of sex. Low birth weight boys who experienced faster growth had the same increase in BMI compared with high birth weight boys.

In other studies, birth size did not affect the association of rapid weight gain and child overweight. Stetter et al. determined that rapid weight gain in the first four months influenced obesity at age seven years, independently of birth weight. However, Hui et al. commented that an effect may not have been observed due to loss of statistical power as a result of a dichotomous outcome and large number of groups of birth weight and growth.

A potential problem in measuring the effect of birth size on the infant growth to child overweight relationship is the change in infant growth being related to initial value or, in this case, birth size. This may attenuate the actual effect of birth size since it is also included in the change-in-infant growth equation. Statistically speaking, the error term of the regression model will be included on both sides of the equation. Most studies that examined infant growth, measured change in weight from birth, which justifies the need to re-examine the effect of birth size removed from the change equation.

1.6 The Role of Accelerated Growth on Birth Size and Child Overweight

Does postnatal growth or magnitude of centile crossing influence health in its own right? Is it growth itself in the causal pathway or is it a modifying factor based on the nature of fetal programming? Recent literature has debated whether change in body size or accelerated infant growth modifies the relationship of birth size and child obesity. Does the effect of growth vary depending on birth size? In a study of low-
income, Mexican children with low and normal BMI z-scores at birth and an accelerated growth pattern during the first year of life, the children experienced increased odds of overweight at age 4 to 6 years. This study adjusted for gestational age, child age, child sex, maternal BMI, maternal height, and family socioeconomic status.\textsuperscript{31} Children who were born small (BMI z-score at birth) or of normal size and who had experienced a positive BMI z-score change of + 1 z-score unit in the first year of life had higher odds of being overweight (OR = 3.58, 95\% CI: 1.68 – 7.44) and obese (OR = 2.23, 95\% CI: 1.12 – 4.46) compared to children who were born small or normal size and who did not experience a positive change in BMI z-score. This relationship did not hold true for infants with a larger BMI at birth.\textsuperscript{31} Length-for-age z-score at birth and change in length-for-age z-score were positively associated with BMI z-score age. However, the relationship of length-for-age z-score and BMI z-score at age 4 to 6 years was not moderated by change in length-for-age score from birth to one year of age. A limitation of this study is the small sample size (n = 163).

1.7 Other Factors Influencing Birth Size and Child Overweight

1.7.1 Socioeconomic Status (SES)

In NHANES, 2005 – 2008,\textsuperscript{124} children and adolescents from lower income families were more likely to be obese compared with children from higher income families. However, these relationships were not consistent across race and ethnic groups. In addition, as education levels increased in the household, child obesity decreased for boys and for girls of non-Hispanic White and non-Hispanic Black ethnicity.

1.7.2 Race/Ethnicity

Racial/ethnic group representation in most of these studies was White with one study done in Asians,\textsuperscript{87, 93} and one in Mexican American children.\textsuperscript{31} Birth weights have been found to vary by race/ethnicity.\textsuperscript{125} Birth weight from birth certificates (1968 – 1972) for Oahu, Hawai‘i, reviewed by Crowell et al.\textsuperscript{125} ranked race/ethnic groups, based on the mean birth weights, from heaviest to least heavy. Whites ranked the highest followed by Native Hawaiian, Japanese, and then Filipino. In a later study by Crowell et
al., Samoans had the largest mean birth weight whether based on single or mixed race/ethnic percentages, among other race/ethnic groups (Whites, Chinese, Filipino, Native Hawaiian, and Japanese). Tam et al. indicated a possible genetically-based race/ethnic difference with regards to age at reaching peak BMI. Chinese/Filipino children reached their peak BMI at six months in comparison with Swedish children who reached their peak BMI between 12 – 15 months. Further research is needed to clarify the relationship of race/ethnicity to birth size, rapid infant growth, and child obesity in a multiethnic population.

1.7.3 Maternal Factors

Birth size is determined by prenatal factors such as maternal BMI, pregnancy weight gain, Gestational Diabetes Mellitus (GDM), smoking during pregnancy, and age at first pregnancy. Genetic factors partially control human growth patterns, which may suggest reasonable relationships between parental BMI and child obesity. In the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort study, the observed risk for obesity at age seven years, was three to four times higher if one parent was obese and 10 times higher if both were obese.

Maternal adiposity and BMI are directly associated with offspring birth weight, with stronger association for the mother compared to the father. However, a recent study by Freeman et al. determined that the odds for child obesity increased in children who had an overweight father (OR = 4.18, 95% CI: 1.01 – 17.33) or obese father (OR = 14.88, 95% CI: 2.61 – 84.77) and healthy mother. This study suggests that the father could also be a potential and novel point of intervention. A limitation to this study is the use of self-reported weight and height which are not always valid in comparison with measured weights and heights. Semmler et al. reported that parental leanness is protective against the development of overweight in children, independently of family SES. Parental obesity is a risk factor for child overweight, especially in lower SES families, which may be attributable to food insecurity and a relatively energy dense quality of the diet.
Mothers who begin pregnancy overweight or obese have a higher chance of having children born with a higher birth size or large-for-gestational age and their offspring are at increased risk for obesity during childhood, adolescence, and adulthood. High levels of glucose and insulin due to high maternal pre-pregnancy BMI result in increased newborn weight.

Excessive weight gain during pregnancy is also closely related to maternal pre-pregnancy BMI, higher birth weight and risk for child overweight. Excessive weight gain during pregnancy is associated with increased risk of overweight at age three years (OR 4.35, 95% CI: 1.69 – 11.24). Weight gain, especially during the first trimester, was associated with child BMI at age five years.

GDM is associated with infant birth weights greater than 4000 g or large for gestational age (> 90th percentile for gestational age). Studies by Pettitt et al. report the presence of obesity at ages 5 to 19 years in Pima Indian infants born to mothers who have GDM. However, in a recent systematic review, 12 studies (years 1998 – 2010) were included and reported crude ORs ranging from 0.7 – 6.3; eight of these studies did not show a significant relationship between maternal GDM and infant birth weight. Only two studies adjusted for pre-pregnancy obesity, which resulted in attenuation of the estimates and no statistical significance. However, Andegiorgish et al. published a new study since the systematic review and reported an increased odds for child overweight (OR = 2.76, 95% CI: 1.37–4.50) in 3,140 Chinese students (age 7 to 18 years) who were born to women positive for gestational diabetes.

Maternal smoking during pregnancy has been associated with an increased risk for child overweight, independently of its relationship with reduced birth weight. Several mechanisms are postulated: 1) direct influence of nicotine on hypothalamic function related to appetite of the fetus and/or infant, 2) weight gain that is associated with nicotine withdrawal which is also seen in adults who stop smoking, 3) and decreased placental and fetal hormones, such as growth hormone, insulin-like growth factor, and leptin. Tobacco compounds, such as nicotine, are also readily available to the infant through breast milk from the mother who smokes. In particular, mothers who smoke during pregnancy have increased risk for low birth weight infants who
also experience later catch-up growth. Rapid catch-up growth has been found to be related to child overweight and obesity.

Alcohol consumption during early pregnancy is associated with fetal growth restriction resulting in low birth weight and in later pregnancy can affect prenatal and postnatal growth. This is due to the decreased cell proliferation in early fetal life and inadequate nutrient uptake causing malnutrition in the latter part of pregnancy.

Preterm deliveries, due to multiple births and maternal parity are also related to low birth weight. Infants who were born of primiparous mothers had lower birth weight, higher birth lengths, and smaller head circumferences than infants born of multiparous mothers. First-born status is associated with overweight at seven years. In addition, rapid growers were more likely to be first-born than less rapid growers.14

1.7.4 Infant Feeding

Greater growth velocity has been noted in infants who have been formula-fed in comparison to breast-fed infants. Breastfeeding has been associated with lower weight gain in infancy and with less obesity in childhood and adolescence than formula feeding; and, the weight gain pattern varies somewhat, with earlier weight gain among breastfeeding infants. This may be due to greater protein content in formula than in breast milk and behavioral factors, such as greater infant regulation of the feeding during breastfeeding.

Increased dietary protein in infant formula may promote excess fat gain by inducing insulin secretion. In the Early Nutrition Programming project, infants consuming a low protein formula (similar to breastfeeding) had slower growth rates and lower BMI at two years of age compared to infants on a high protein formula. In addition, shorter duration of breastfeeding has been associated with increased risk of childhood obesity. On the contrary, Dennison et al. reported that the association between rapid infancy weight gain and obesity development was the same between formula-fed and breast-fed babies. Another study reported that breastfeeding is associated with faster weight gain in the first six months compared to formula feeding, and only later in infancy did breast-fed infants have lower weights. Among 124
infants fully breast-fed for ≥ four months, no significant differences were found between rapid growers and normal growers, although the direction of association was positive (protective) for risk of overweight at age seven years, similar to what has been found in other cohorts.83, 179

1.8 Literature Summary and Research Gap

The state of research on the relationship between birth size and rapid infant growth with child overweight provides supportive evidence for a positive association of both variables with child overweight. However few studies have adequately examined components of birth size (birth weight, length) or proportionality (e.g., weight-for-length), or adjusted for gestational age. Nor have studies included many non-White ethnic groups, or examined obesity outcome at age five years, a critical age in the lifespan as a child transitions to school.

Contributions of prenatal (maternal factors) or postnatal (birth size and accelerated growth) factors on the risk of child overweight require further study. These differences can be further teased apart by examining whether birth size or accelerated growth modifies, or rate of infant growth mediates, the positive association of birth size and child overweight. Examining these relationships will provide direction for development of future interventions. It is essential to look at these sensitive periods of growth, where effects of certain exposures are limited to one particular stage of growth. Health services data that provide longitudinal information related to mother, infant, and child overweight status provide opportunity to look at these relationships.

Therefore, further research is needed, specifically, to examine: 1) the association of birth size and child overweight adjusted for gestational age and maternal factors, 2) the association of infant growth (as measured by gain in weight, length, and weight-for-length gain) and child overweight with adjustment for birth size (birth weight, birth length and birth weight-for-length) and gestational age in a multiethnic population, 3) the role of infant growth (mediation or moderation) on the association of birth size and child overweight.

The format of the infant growth variable for analysis (continuous or categorical) also varied among previous studies. Categorization of growth and obesity is often based
on cut points which are arbitrary and may not be applicable to all populations. Growth is a biological process which should initially be examined as a continuous measure. Separating the effects of birth size from the change-in-infant growth equation should also be tested. Finally, further exploration of sex and ethnic differences in birth size and its influence on infant growth patterns may explain differences in overweight prevalence.

Longitudinal data provided through the Kaiser Permanente Hawai‘i (KPH) Electronic Medical Record (EMR) system provide retrospective, measures to study growth and overweight in early childhood. In addition, the data structure provides the ability to adjust for maternal and postnatal confounders which were not available in previous longitudinal birth cohorts.

1.9 Significance/Rationale

Growth during childhood has been proposed as a possible linkage between fetal growth and risk for adult diseases.\textsuperscript{50, 87, 97} Child overweight is associated with early maturation, adolescent and adult overweight and subsequent risk for type 2 diabetes, cardiovascular disease (CVD), musculoskeletal disorders, certain cancers, and overall mortality. The importance of drawing links between factors associated with child overweight and subsequent health risks in adulthood has become increasingly evident. Studies of recent, multiethnic cohorts are needed to understand further race/ethnic differences in birth size, growth patterns, and risk for overweight and health disparity related to these factors.

Growth is a basic developmental process for children, and it is a period of life that is strongly influenced by many factors. Recent literature suggests a need for exploring these factors, including weight, length, and BMI gain. Furthermore, identification of early nutrition and growth patterns as markers for intervention is key to program planning for prevention and better treatment of child overweight. Obesity is occurring in increasingly earlier childhood; and, prevention, prior to the onset of puberty, will permit continued growth that will support optimal health. The present study will examine the relationship of birth size to rate of infant growth and the relationship of both variables to risk of childhood overweight in the multiethnic KPH population.
1.10 Study Goal
To elucidate further the relationship of birth size and rate of infant growth to child BMI at age five years in a multiethnic population. The specific aims for this study are described in Table 1.6 and conceptualized in Figure 1.2.

Table 1.6. Specific Aims

<table>
<thead>
<tr>
<th>AIM 1</th>
<th>Is birth size associated with child BMI at age 5 years?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H_0 = \text{Birth size is not associated with child BMI at age 5 years.}$</td>
</tr>
<tr>
<td></td>
<td><strong>Based on Literature:</strong></td>
</tr>
<tr>
<td></td>
<td>Higher birth size is associated with higher BMI at age 5 years.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIM 2</th>
<th>Is change in infant growth associated with child BMI at age 5 years?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H_0 = \text{Change in infant growth is not associated with child BMI at age 5 years.}$</td>
</tr>
<tr>
<td></td>
<td><strong>Based on Literature:</strong></td>
</tr>
<tr>
<td></td>
<td>Greater change in infant growth is associated with higher BMI at age 5 years.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIM 3</th>
<th>Is the effect of birth size on BMI at age 5 years mediated by change in infant growth?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H_0 = \text{The effect of birth size on BMI at age 5 years is not mediated by change in infant growth.}$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIM 4</th>
<th>Is the effect of birth size on BMI at age 5 years modified by change in infant growth?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H_0 = \text{The effect of birth size on BMI at age 5 years is not modified by levels of infant growth}$</td>
</tr>
<tr>
<td></td>
<td><strong>Based on Literature:</strong></td>
</tr>
<tr>
<td></td>
<td>Small and average birth weight is associated with faster rate of infant weight gain and higher BMI at age 5 years.</td>
</tr>
</tbody>
</table>
Figure 1.2. Conceptual Framework of Present Study
CHAPTER 2. METHODS

2.1 Study Design

The study design is a retrospective, longitudinal study using the KPH EMR. The dataset for this study is part of a larger dataset provided for the Pacific Kids DASH for Health (PacDASH) study.

The PacDASH study is a four-year, United States Department of Agriculture (USDA) funded study, (Rachel Novotny, PI, : 2008-55215-18821 (2/15/2008 – 2/14/2012) under the Cooperative State Research, Education, and Extension Services, National Research Initiative (NRI) Competitive Grants Program Award [now National Institute of Food and Agriculture (NIFA) and Agriculture and Food Research Initiative (AFRI)]. PacDASH is comprised of two main objectives: 1) to develop a community-based participatory intervention that links food, physical activity, and health which targets children (> 50th – 99th BMI-for-age and sex percentile, ages 5 – 8 years) in Hawai‘i with a goal of preventing further weight gain, and 2) to describe environmental, social, economic, and cultural factors associated with child overweight in the KPH population by using secondary data from the KPH EMR.

Objective #2 also aims to understand the ecological framework of child obesity and factors that are known or hypothesized to influence the development of child obesity in Hawai‘i’s multicultural population. Objective #2 data are being examined in two ways: a) an expansion of the PacDASH intervention sample to include other children and information on early life factors that may influence later overweight for cross-sectional and later prospective analysis, and b) estimation of the relationship between birth size, infant growth and child overweight risk at age five years (see Figure 2.1).

2.2 Study Population and Sampling

KPH is a non-profit integrated health care system that provided health care in 2011 to about 19% of the employed population of Hawai‘i (~220,000 members).\(^{180}\) The KPH membership covers a wide range of socioeconomic backgrounds, from professional to blue-collar worker, and 10% of the membership receives coverage from Medicare/Medicaid or Quest, the state insurance program.\(^{180}\) KPH provides medical
care in 18 outpatient clinics on Oahu, Hawai‘i, and Maui, and in a 235-bed hospital located on the island of Oahu. KPH membership is ethnically similar to the general Hawai‘i population. Table 2.1 shows a comparison of Hawai‘i state data on sex and racial/ethnic distribution$^{181}$ with KPH data estimated through an EMR sample in 2011. KPH coordinates and maintains patient care documentation in the EMR and in online communication systems, with a comprehensive EMR interface referred to as HealthConnect®. KPH HealthConnect® coordinates patient care which includes information on all visits, procedures, diagnoses, hospitalizations, membership types, and demographics of plan members.$^{182}$ This innovative tool further prevents regular occurrence of incomplete, missing, and unreadable charts. The EMR system began in KPH in 2004, and became fully operational in 2005.

---

**Figure 2.1.** Sampling Framework

Objective 1
PacDASH
Intervention Study
Children
Ages 5 to 8 years
Born in 2002 - 2005
n = ~8,000

Objective 2a
PacDASH EMR
All KPH children
Ages 5 to 8 years
Born in 2002 - 2005
n = ~8,000

Objective 2b
OSHIRO
Dissertation
Children
Ages 4 to 6 years
Born in 2004 - 2005
n = ~100
EMRs provide benefits to both patients and providers in health care delivery systems. They also provide observational data from clinical practice that can be useful for researchers interested in investigating practice patterns and in evaluating quality indicators, disease rates, and longitudinal trends. EMR data have also become a useful tool for conducting health services and epidemiologic research. Understanding ways to analyze such data, with consideration for internal and external validity, continues to be a part of the research. Since 1998, intensive efforts have been made to standardize medical terminology, clinical data, and units of measures in EMR data. However researchers still need to identify and account for measurement error.

KPH is a member of the Health Maintenance Organization Research Network (HMORN) which consists of a membership of 19 HMOs across the United States. The Virtual Data Warehouse (VDW) is an existing resource of data developed by the HMORN which provides standardized coding terms across health systems in order to allow comparisons of data among 15 of the 19 sites. These data are derived from data tables that exist under the HealthConnect® Interface of the KPH EMR. Figure 2.2 depicts the flow of information gathering from members to research data tables.
Variables exist in different HealthConnect® tables which are identifiable for research in the VDW. Existing tables used for this study include: Patient (demographics, geocoding), Vitals (repeated measures or observations), Baby Birth, and Maternal/Pregnancy data tables (Figure 2.3).

2.2.1 Inclusion Criteria

To estimate the association of birth size, infant growth, with child overweight, data requirements include the following inclusion criteria for this retrospective study:

- all children who are current members of the KPH HMO as of January 2010, and who were born in 2004 – 2005 at KPH
- birth information (birth weight, birth length, gestational age)
- weight and height measures at three time points (2 to 4 months, 22 – 24 months, 4 to 6 years)
- singleton births

2.3 Description of Birth Measures and Data Cleaning

Since EMR data are not collected initially for research purposes, in a controlled research environment, it is especially important to consider sources of error before data analysis. In addition, weights and heights are measured by health care professionals in different clinics which likely increases error, and results in decreased power to detect associations. This study applies a systematic data cleaning process that is relatively new, given the short era of electronic medical record systems.

KPH data were examined for biologically implausible values of birth size and infant weight and length/height information which included univariate and bivariate analysis (e.g., plotting of gestational age and birth weight) for identification of outliers. Assessment of linear regression assumptions including multivariate normality were also assessed by checking the variance and distribution of the residuals of study models.
Figure 2.2. Data Flow: Clinic to EMR to Research
CLARITY TABLES

DATASETS*

- Encounter
- Patient
- Virtual Data Warehouse (VDW)
- Ob History

Vitals
Demographics/Geocode
Baby Birth
Maternal Pregnancy**

In Progress

*Datasets are linked by a unique ID – Child Medical Record Number
**Child needs to be linked with mom for maternal/pregnancy information

Figure 2.3. Existing KPH EMR Data Tables for Research Dataset
2.3.1 Birth Size Variables (Birth Weight, Birth Length) and Gestational Age

Steps for cleaning birth size variables (birth weight, birth length) and gestational age

1) Check biological plausibility of values (Univariate analysis)
   a) Examine distribution of birth weight, birth length, and gestational age
   b) Determine biologically plausible ranges for birth size categories based on plausible values described in literature and clinical practice
   c) Examine values above and below biologically plausible values
   d) Examine values with unique birth weight, birth length, and gestational age
   e) Remove unique medical record numbers (MRN) with outlying values

2) Check for invalid proportionality (Bivariate analysis)
   a) Perform visual inspection by plotting birth weight by birth length, birth weight by gestational age, and birth length by gestational age
   b) Compare invalid proportions with those identified through reference proportion categories for birth weight and gestational age
   c) Remove unique MRNs with outlying values

3) Check for degree of deviation from the regression line (Multivariate normality)
   a) Fit regression model to obtain residual information (e.g., BMI = birth weight, gestational age, birth length)
   b) Run univariate analysis on residuals
   c) Remove unique MRN for those with SD > 4.0

2.3.1.1 Birth Weight

Birth weight is a function of length and of pregnancy duration, or gestational age (e.g., fetal growth) and thus the two variables are correlated. However, these factors are not interchangeable due to differences related to risk, etiology, and consequences. Birth weight is defined as the “weight of fetus or infant at delivery” and is recorded in grams, or pounds and ounces. It is also viewed, conceptually, as a measure of the extent of maturity and physical development of the fetus and may be influenced by genetic predisposition or prenatal environmental exposures. Birth weight is an indicator of
newborn infant survival or risk for early morbidity. Live births in 2001 – 2002 to US resident mothers identified median birth weight for singleton, full-term live birth babies as 3,487 g and the mean birth weight was 3,303 g. \textsuperscript{91} Low birth weight refers to the weight of an infant at delivery regardless of gestational age or length and is defined as weighing less than 2,500 g. \textsuperscript{91,187} The following further classifications of low birth weight have been established to identify high risk infants: Moderately Low Birth Weight (1,500 – 2,499 g), Very low birth weight (< 1,500 g), Extremely Low Birth Weight (<1,000 g). High birth weight, or macrosomia, is defined as > 4,000 g. \textsuperscript{91,188}

In KPH, birth weights are measured and entered as grams at birth and then are electronically converted to ounces in HealthConnect\textsuperscript{®}. Birth weights were electronically converted back to grams for analysis. A total of 5,074 children born at KPH from 2004 to 2005 had birth weight information. To adjust for gestational age, the sample was limited to include those who had both a recorded birth weight and a gestational age (n = 4,271).

In Step #1, lower and upper limits of birth weight were estimated and frequencies were run, starting with a lower limit of 454 grams (1 lb). First year survival has been estimated at 51% for children born < 454 grams (1 lb). \textsuperscript{189} The upper limit was initially set at 4,536 grams (10 lbs) to examine the upper range of values.

Values were continuous and close to each other until about 5,443 g (12 lbs); birth weight values then rose to numbers that were implausible (> 9,752 g, 21.5 lbs). Therefore, based on plausible values as described, the birth weight range was set at > 454 g and < 5,443 g. Two children were removed from the sample (values of 9,752 and 35,380 g) at Step #1 resulting in a sample of n = 4,269 with plausible birth weights.

2.3.1.2 Birth Length

At KPH, birth lengths are measured and entered into HealthConnect\textsuperscript{®} as inches at birth. Birth length was electronically converted to centimeters. Of the 5,074 children born at KPH, 3,707 had a birth length value, and 1,367 were missing birth length information.

Univariate analysis indicated a large jump among the lowest extreme observations from 2.04 to 18.79 cm. Two children were removed with values less than 18.79 cm
(0.46 cm and 2.05 cm). Upper end estimates indicate continuous values from 18.79 to 63.5 cm. Twenty children were removed with values ranging from 99.1 to 254 cm. A total of 23 children were removed at Step #1 resulting in a sample of n = 4,246.

2.3.1.3 Gestational age

Gestational age is typically defined as the length of time in weeks from the first date of a women’s last menstrual period (LMP) to the date of the infant’s birth.\(^91\) This interval has served as the gold standard for determination of gestational age and has been used in validation studies with alternative methods for measuring gestational age.\(^91, 190\)

Limitations to using LMP for estimating gestational age include overestimation of the duration of pregnancy by two weeks, inaccuracies of poor recall of LMP, or early menstrual spotting in pregnancy.\(^191\) Other methods include ultrasound dating and developmental assessment. Ultrasound dating commonly uses reporting software that calculates a composite gestational age using measurements of biparietal diameter (BPL), Head Circumference (HC), Abdominal Circumference (AC), and Femur Length (FL) conducted before 22 weeks of pregnancy. However, ultrasound predictions of gestational age becomes less accurate as pregnancy progresses due to individual variations in fetal growth and environmental exposures.\(^192\) In addition, women facing barriers to prenatal care, may be less likely to have ultrasound measures, especially in developing countries; and, the quality of ultrasound equipment and level of training of ultrasound technicians may vary across care. Thus, the use of a growth estimate of gestational age during pregnancy while studying an outcome of growth also introduces error. A postnatal method (Ballard method) for determining gestational age includes a developmental assessment and scoring system of physical and neurological characteristics of the newborn (infant weight, length, head circumference, condition of skin and hair, reflexes, muscle tone, posture and vital signs) devised by Dubowitz and coworkers\(^193\) and later modified by Ballard et al.\(^194\) Concerns for utilizing this method are the accuracy for use in preterm and very preterm infants and application to different race/ethnic groups. Current epidemiological studies use the LMP or with the clinical estimate of LMP as reported on birth certificates.\(^91\)
Data cleaning criteria for gestational age include the age at fetal viability or age at which the fetus is able to survive outside of the womb.\textsuperscript{195,196} Babies born at 23 weeks may survive with access to a state-of-the-art Neonatal Intensive Care Unit (NICU), but the odds of survival are low. A baby born at 24 weeks would generally require extensive intervention, potentially including mechanical ventilation and other invasive treatments followed by a lengthy stay in a NICU. Twenty-four weeks is the lowest age cutoff point for which physicians will use intensive medical intervention to attempt to save the life of a baby born prematurely.\textsuperscript{189}

In KPH, gestational age at delivery is measured in weeks. Gestational age is based on the last menstrual period and is updated with ultrasound measures and time of actual delivery. Of the 5,074 children born at KPH, 4,271 had a gestational age value and 803 had missing gestational age information.

Of the current sample, one child had a value less than 24 weeks (23.5); this child was included in the sample since the age was close to the lowest age of fetal viability (23 weeks). Most deliveries occur prior to 42 weeks or the pregnancy is induced to decrease risk for complications that can occur due to circumstances, such as decreased amniotic fluid and decreased function of the placenta. Two children were delivered at 44 weeks gestation and were included in the sample. It is plausible that a child be delivered after 42 weeks, which is considered a post-term pregnancy, if the mother did not select elective delivery at 42 weeks.\textsuperscript{197} Two children had an erroneous value of three weeks and 99 weeks and therefore were not included in the sample. The selected gestational age range for this sample was 23 to 44 weeks, which will be examined as a continuous variable. Two children were removed at Step #1 of data cleaning resulting in a sample of 4,244.

Clinically, gestational age has been categorized into Preterm (< 37 weeks), Term (37 – 41 weeks) and Post term (> 42 weeks) for the purpose of assessing health risks associated with gestational age and fetal growth.\textsuperscript{91} Further sub-categories have been developed to assess risk of early or late gestational age and fetal growth and are used on a population basis to determine need for services: small-for-gestational age term (37 – 40 weeks gestation < 10\textsuperscript{th} percentile of birth weight for gestational age), average-for-gestational age (10\textsuperscript{th} – 90\textsuperscript{th} percentile of birth weight for gestational age), and large-for-gestational age (> 90\textsuperscript{th} percentile of birth weight for gestational age). Clinically, these
classifications are useful guidelines for assessment of risk. However for research purposes, arbitrary cut points assume “one-size fits all” and may not fit for populations different from those used to derive the clinical cut point. For the purposes of adequately describing the birth size distribution of the KPH population, all levels of birth weight and gestational age were retained. Future work will include describing the population in these categories as they apply to clinical practice.

Step #2 in birth size cleaning included visual inspection of bivariate plots. This was done by plotting birth weight and birth length by gestational age and also by checking outliers identified by comparison with a referenced method for inclusion of plausible birth weight and gestational age data. Initial bivariate plotting and visual inspection of birth weight by gestational age identified five cases that had an implausibly high birth weight (2,900 – 4,000 g) for gestational age (< 31 weeks). These five cases were verified using the reference method which resulted in exclusion of the same cases. Three cases had a low birth weight (< 1,800 g) for gestational age (> 38 weeks), two cases had a high birth weight (> 3,000 g) for birth length (< 24 cm); nine cases had a low birth weight (< 2,800 g) for birth length (29 – 40 cm). A total of 19 cases were removed based on bivariate plotting resulting in a sample of n = 4,227.

With step #3, seven cases differed from their expected value by more than 4.0 SD and were removed from the study sample. After cleaning step #1, #2, and #3, a total of 53 EMR (27 in step #1, 19 in Step #2, 7 in step #3) had been removed as possible errors in birth measures, resulting in a total of n = 2,946 children with all three clean measures of birth weight, birth length, and gestational age. Mean birth size and gestational age measures before and after cleaning are described in Table 2.2.
Table 2.2. Mean Birth Weight, Birth Length, Gestational Age

<table>
<thead>
<tr>
<th>Before Cleaning</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)(^a)</td>
<td>5074</td>
<td>3292 ± 745</td>
<td>546</td>
<td>35380</td>
</tr>
<tr>
<td>Birth Length (cm)(^b)</td>
<td>3707</td>
<td>49.8 ± 7.3</td>
<td>0.5</td>
<td>254</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>4271</td>
<td>38.6 ± 2.4</td>
<td>3</td>
<td>99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>After Cleaning</th>
<th>N</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>4221</td>
<td>3264 ± 597</td>
<td>546</td>
<td>5103</td>
</tr>
<tr>
<td>Birth Length (cm)</td>
<td>2946</td>
<td>49.2 ± 3.2</td>
<td>30.5</td>
<td>58.4</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>4221</td>
<td>38.6 ± 2.1</td>
<td>24</td>
<td>44</td>
</tr>
</tbody>
</table>

\(^a\)grams, \(^b\)centimeters

2.4 Infant Growth Data

2.4.1 Selection of Infant Weight and Length Data

The first two years of life were selected as the time period for measuring rate of growth since this is a critical time period related to child and later overweight.\(^{159}\) Catch-up growth begins within the first three postnatal months and is completed by about 12 – 18 months whereas catch-down or “compensatory deceleration”\(^{198}\) of normal growth starts a little later and may not be complete until 18 – 24 months.\(^{199,200}\) It is important to consider any crossing of growth percentiles during this time period for early recognition of, and efforts to, prevent obesity. Thereafter pre-pubertal growth is stable on the trajectory established during the previous infant period.\(^{200}\)

To assess infant growth, weight and length measures from scheduled well child visits were utilized. KPH has a schedule of well child visits that aligns with suggested immunizations and supports monitoring of normal growth and development. These well child visits are scheduled at 1 week after birth, 2, 4, 6, 9, 12, 18, 24, 36, 48, 60, 72 months, and every two years thereafter. Calendar dates of well child visits vary by child, however many well child visits do occur during the recommended months for well child visits (Figure 2.4). The much higher attendance at the 60 month visit is related to immunization requirements for school admission.
Rate of infant growth is defined as change in infant weight and length per unit time. To measure change, data were sampled in two age ranges: early infancy (2 to 4 months) and at the end of infancy (22 to 24 months). A starting point of two months was selected as distant enough from the birth period, in order to separate its effect from the influence of birth size on infant growth. A range of months was created to capture all possible weights and lengths. Children scheduled for the two month well child visit might come in anytime from the start of the 2\textsuperscript{nd} months (62 days) through the 4\textsuperscript{th} months (124 days), end of the 22\textsuperscript{nd} months (682 days) through the 24\textsuperscript{th} months (744 days), and from the 4\textsuperscript{th} year (1,461 days) up to the 6\textsuperscript{th} year (2,155 days). If several measures were taken within each age range per individual child, data cleaning processes were conducted and the last measure by MRN, per time period, was used for consistency. To account for differences in duration of time between visits, change in weight or length was divided by change in age in months (infant period = 2 to 24 months).

* From cleaned sample of birth weight and gestational age n = 4,106 (4,252 total, 146 missing).

Not all months are featured, mainly well child visits.

**Figure 2.4.** Number of Children Attending Well Child Visits by Child Age in Months in the sample (n = 1,477*)
2.4.2 Cleaning of Infant Weight and Length Data

Standard clinical practice guidelines for measuring infant length are to measure supine length in children up to 24 months and standing height or length or both from 24 to 26 months. Standing height is less than recumbent length with mean differences ranging from 0.4 to 2.3 cm between 18 and 36 months of age. Although measuring supine length is a recommended practice guideline, this may not be consistently followed if the child is able to stand before 24 months. This is a limitation that is acknowledged; however, only weights/lengths up through 24 months were examined, which would decrease the number of children measured using standing height.

Electronic medical records are used in routine medical care. This type of monitoring is not without risk of data entry error. A study investigated error rates of electronic weight and height data of children aged 0 – 18 years receiving care at Kaiser Permanente Southern California and found low error rates [children < 2 years (0.4%); 2 – 5 years (0.7%); 6 – 9 years (1.0%); 10 – 13 years (1.0%); 14 – 18 years (0.7%) after excluding implausible values].

To decrease error, weight and length data for this study were obtained only from well child care visits, an encounter code in data tables. This assures that weights and lengths were obtained from the pediatric or family practice departments, which are more practiced with performing these measures, and not from other departments (e.g., Emergency room visits).

The first step in infant weight and length data cleaning was to identify biologically implausible values (BIV). A SAS program for CDC growth charts was used to identify outlier observations. This program is recommended for use by the HMO Obesity Research Network Subgroup. The program uses z-scores to determine out-of-range values in a population. It is very common for these implausible values to be based on data entry or measurement error rather than extreme growth values. The WHO provides the recommendations on outlier cut-offs based on the 1977 National Center for Health Statistics (NCHS)/WHO growth charts which have been used worldwide for anthropometric measurement. Two methods are recommended: 1) the flexible exclusion
range: 4 z-score units from the observed mean z-score, with a maximum height-for-age z-score of +3.0 and 2) the fixed exclusion range:

- weight-for-age, < -5.0 and > +5.0
- height-for-age, < -5.0 and > +3.0
- weight-for-height < -5.0 and > +5.0

Flags are created on a linear scale so that their performance at extreme values can be mathematically calculated. The SD is calculated above and below the median. This is calculated by taking half the difference between 2 z-scores and 0-score points. A flag is then calculated using the “fixed” SD. For example, if a flag < - 5.0 SD for weight-for-age then Biologically Implausible Values for Weight (BIVWT) = 1 (too low) and if a flag > 5 then BIVWT = 2 (too high). A BIVWT of 0 = normal range. The fixed exclusion range for weight-for-height z score equaled < - 4.0 and > 5.0 and this range can also be applied to BMI-for-age.

The second step in infant weight and length cleaning included checking for implausible values within the biologically acceptable range of values for individual observations. This was determined by:

1) Calculating a variable that measures the difference between each measure (excluding the first observation).

2) Calculating days between each measure and units per week (e.g., g/gained/week).

3) Comparing with guidelines for average weight or length gains. (Limit the sample to the difference greater than or less than average expected gain for this age range).

4) Examining data for gross differences in weight or length.

For example, an infant might be expected to gain about 140 to 200 g (0.14 to 0.20 kg per week) in the first six months and to double his/her birth weight by about five months. The most weight gain expected on average is a 1.1 – 1.6 kg gain in two months. Limits were set on any difference in weight greater than 2 kg gain and less than 1 kg loss.
Negligible weight losses are expected due to recording errors\textsuperscript{203} or possibly due to a child being sick. However since children are growing, observation of a large loss in length is not expected. If a difference in weight or length was questionable, average weight gain or loss/week was examined to determine the plausibility of the finding. Further visual inspection of the sequence of weight or length/height measures within individuals was completed to gain a better understanding of the reason for large differences. In most cases, large differences ($> 3$ kg) were due to gross error between measures. Table 2.5 illustrates an example of what is commonly seen.

**Table 2.3. Example of Invalid EMR Recording of Weight for a Child**

<table>
<thead>
<tr>
<th>Measure Date</th>
<th>Age in Months</th>
<th>Weight (kg)</th>
<th>Difference in Weight (kg)</th>
<th>Difference in Days</th>
<th>Weight(kg)/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 19</td>
<td>3.02</td>
<td>6.84</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>March 22</td>
<td>3.12</td>
<td>7.08</td>
<td>0.16</td>
<td>3</td>
<td>0.0228</td>
</tr>
<tr>
<td>March 26</td>
<td>3.25</td>
<td>3.09</td>
<td>-3.99</td>
<td>4</td>
<td>-0.57</td>
</tr>
<tr>
<td>March 29</td>
<td>3.35</td>
<td>7.14</td>
<td>4.05</td>
<td>3</td>
<td>0.58</td>
</tr>
<tr>
<td>April 28</td>
<td>4.30</td>
<td>7.65</td>
<td>3.6</td>
<td>30</td>
<td>0.12</td>
</tr>
</tbody>
</table>

In the case where the erroneous value was the last observation that would be selected for that period, the value was set to missing and the previous value was selected. These values were also rechecked to assure plausible weight or height selection. The same method was completed for weights and lengths/heights for two time periods: 22 – 24 months and the 4 to 6 years.

Decision rules for visual inspection are:

1) If the previous value of the last measure of the child was implausible, the last measure was still valid and therefore the child was left in.

2) If the previous value within age range was a plausible measure then the invalid measure was set to missing and selection was based on previous valid measure.
3) Measures were rechecked to assure plausible weight or height selection.
4) If the last value of the child was an implausible measure and there were no previous plausible values within the age range, the child was excluded.

Most erroneous values were removed through the CDC SAS program. Most visual inspection cases fell within decision rules 1 and 2 (14 cases). Only one unique observation was deleted because it met decision rule #3. Total records removed from cleaning steps for infant growth data are summarized in Table 2.6.

### Table 2.4. Data Cleaning of Infant Growth (Weight and Length/Height)

<table>
<thead>
<tr>
<th></th>
<th>Period of Growth</th>
<th>Step 1 CDC</th>
<th>Step 2 Visual Inspection</th>
<th>Total removed</th>
<th>Total missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>2 to 4 mo</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>22 to 24 mo</td>
<td>11</td>
<td>1</td>
<td>12</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>4 to 6 y</td>
<td>22</td>
<td>0</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>Length/Height (cm)</td>
<td>2 to 4 mo</td>
<td>33</td>
<td>0</td>
<td>13</td>
<td>871</td>
</tr>
<tr>
<td></td>
<td>22 to 24 mo</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>673</td>
</tr>
<tr>
<td></td>
<td>4 to 6 y</td>
<td>37</td>
<td>0</td>
<td>37</td>
<td>6</td>
</tr>
</tbody>
</table>

### 2.5 BMI at Age Five

The outcome variable, BMI at age five years, was calculated with a weight and height taken at a well-child visit between the ages of 4 to 6 years of age. A range of ages was selected since visits usually do not occur exactly at the specific “well child visit age”. Also, since multiple visits could be taken between four to six years of age, the sample was further limited to observations or well child visits that had both a weight and height and utilized the last visit available that had both a weight and a height measurement. BIVBMI values are shown in Table 2.7.

Low BIVBMI values were considered implausible if the BMI was < 13.5 (< 1st percentile; n = 7, BMI range 2.45 – 11.8, Table 2.7). A high BIV value is indicative of a BMI which is > 18 (> 95th percentile; n = 41, BMI range = 23.2 – 64.6, Table 2.7).
High and low BIV values were also examined by ethnic group to see if there was a race/ethnic group relationship with outlying values (Table 2.8). The SAS program for CDC growth charts uses the 2000 CDC growth charts reference. The reference population which has a lower percentage of Asian and Pacific Islander representation than the KPH population. Although the weight-for-height z-score range of inclusion is quite wide, we expect that some race/ethnic groups (e.g., Pacific Islanders, Native Hawaiians) may have a higher BMI than White non-Hispanic children. This is an important consideration to note for future study; nonetheless, the CDC SAS program was used as the reference for removing outlying values due to the absence of an alternative.

Table 2.5. Biologically Implausible Values (BIV) for BMI-for-Age and Sex

<table>
<thead>
<tr>
<th>BIVBMI*</th>
<th>n</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2490</td>
<td>98.11</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td>0.28</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>1.62</td>
</tr>
</tbody>
</table>

*1 = High BIVBMI, 2 = Low BIVBMI

2.6 Covariates and Potential Confounders

Variables were selected to improve the precision of the model or as potential confounders based on the current literature. Improvement in the precision of the model (e.g., adjusting for age) assists in removing variability in the estimate of the exposure on the outcome contributed by other known predictors. Thus, precision of the effect estimate is demonstrated by of narrowing the CI, as a result of controlling for covariates and potential confounders.

2.6.1 Age and Sex

Age in years is calculated as a continuous variable. Female gender was significantly associated with higher child body mass index at age six years. Sex is a categorical variable: Male and Female. Both variables were added to the model as precision variables.
Table 2.6. Low and High BIVBMI by Race/Ethnic Group

<table>
<thead>
<tr>
<th>Race/Ethnic</th>
<th>n</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW BIVBMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2</td>
<td>8.52 ± 3.1</td>
<td>6.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>10.77 ± 1.5</td>
<td>9.7</td>
<td>11.8</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>1</td>
<td>11.4</td>
<td>11.4</td>
<td>11.4</td>
</tr>
<tr>
<td>Other PIa</td>
<td>1</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2.5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>HIGH BIVBMI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1</td>
<td>29.9</td>
<td>29.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Asian</td>
<td>7</td>
<td>27.9 ± 6.1</td>
<td>23.6</td>
<td>39.9</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>17</td>
<td>28.5 ± 9.5</td>
<td>23.7</td>
<td>64.6</td>
</tr>
<tr>
<td>Other PI</td>
<td>12</td>
<td>25.7 ± 2.4</td>
<td>23.2</td>
<td>31.0</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>27.9 ± 1.0</td>
<td>26.2</td>
<td>27.9</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>25.6</td>
<td>25.6</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Note: Other Pacific Islanders

2.6.2 Race/Ethnicity

Child overweight and birth size vary by race/ethnicity. Therefore, since race/ethnicity is associated with both the exposure and outcome, race/ethnicity is a potential confounder. KPH race/ethnic information is gathered from one of three sources: 1) upon inpatient admission via interview, 2) by personal history sheet completed by the parent for the child at all clinics, 3) and as a part of the tumor registry, which uses the above methods, plus physician notes, to assign race/ethnicity. The race fields within the user interface for Health Connect® are now at least 80% populated from these sources, providing the race/ethnicity information for the KPH VDW. The KPH personal history sheet, provides opportunity to fill in more than one race/ethnic category, which is coded as a subsequent race/ethnic variable per individual (race/ethnic variable 1 – 5). Race coding for the VDW race/ethnic variable is based on the methodology used by Surveillance Epidemiology and End Results (SEER). The first race/ethnic variable indicates the first race/ethnic group indicated by member. This first race/ethnic group variable (Race 1) will be used as an initial step to describe race/ethnicity.
For each race/ethnic variable, there are 27 race categories, which were collapsed to six categories for these analyses: Asian, White, Native Hawaiian, Other Pacific Islanders (Other PI), Other, and Unknown. “Asian” included Chinese, Japanese, Filipino, Korean, Asian Indian, Vietnamese, Laotian, Hmong, Kampuchean, Thai, and Other Asian.

“Native Hawaiian” race/ethnic group is coded similarly as the Hawai‘i Health Survey algorithm where any persons who are recorded as a combination of Native Hawaiian and any other race are coded as Native Hawaiian. “Other PI” included Micronesian -none other specified (NOS), Chamorran, Guamanian-NOS, Polynesian-NOS, Tahitian, Samoan, Tongan, Melanesian-NOS, Fiji Islander, New Guinean, Pacific Islander-NOS.

“Other” included Black, American Indian/Aleutian/Eskimo, and Other. “Unknown” indicated that race/ethnicity information was missing.

2.6.3 Socioeconomic Status

Children from lower income families are more likely to be obese compared with children from higher income families. Maternal education was used as a proxy for socioeconomic status and is available through child birth certificate information. It is included as a precision variable and described as the total number of years of education.

2.6.4 Infant Feeding

Breastfeeding has been associated with lower weight gain in infancy and with less obesity in childhood and adolescence than formula feeding. Thus, this variable was included as a potential confounder in Study Aim 2 models. A coded field for breastfeeding is currently not available. Common text/phrases related to breastfeeding available in Smart Sets (a template tool used by clinicians for documentation, coding diagnoses, and ordering tests and procedures) were identified and used for searching the text fields of notes that document the physician’s interaction with the mother. Text search words included “breast”, “breastfed”, “breastfeeding”, “BF”, “nursing”, and “pumping”. These words were searched in well child visit Smart Sets from birth to 24 months. A categorical variable called “breastfeeding status” was created (Breastfed = Y, Not Breastfed = N). Breastfeeding duration was determined by using the last report of
breastfeeding at any encounter minus date of birth and is reported in months. Although this variable does not take into account the fact that women may have breastfed past this last encounter, it provides an indicator of the average minimum duration of breastfeeding.

2.6.5 Maternal Factors

The KPH EMR provides the opportunity to link the child with existing maternal data. Each child was linked by medical record with mother’s medical record which is via parent membership (mother or father) information at Kaiser Permanente. In addition, maternal information gathered on the birth certificate through the Vital Statistics Department at KPH provides supplemental maternal information.

Multiple births such as twins and triplets are associated with different factors and complications during pregnancy. This may be related to birth size and later infant growth. For the purpose of this analysis, only singleton births were included (98% of births).

Mothers who are overweight or obese have a higher chance of having children born with a large birth size and their offspring are at increased risk for obesity during childhood, adolescence, and adulthood. Maternal BMI is both a variable of interest and potential confounder. To calculate maternal BMI, pre-pregnancy weights taken one year before estimated conception date were used as long as the women were not pregnant or did not deliver during that year. In a 2004 Kaiser Women’s Health Survey, 84% of women of child-bearing age reported attending a health care visit in the previous year. However, the available number of pre-pregnancy weights was greater than first pregnancy weights; this is due to the source of maternal weight (paper charts vs. availability of electronic data during the 2003 - 2004 years). Pre-pregnancy weights were mostly measured at their Primary Care Physician (PCP) visit and first pregnancy weights at the Obstetrics (OB) visit. During the birth years of this sample population, (2004 – 2005), the majority of the maternal information for the corresponding pregnancy (2003 – 2004) gathered up to that point was done via paper and was not converted to electronic data. Electronic entry of this information was conducted over time from 2005 in conjunction meeting overall KPH HealthConnect® requirements and Obstetrics-Gynecology (OB-GYN) departmental needs. In these data, there were more pre-
pregnancy weights available (n = 1,120, <365 days) than first pregnancy weights (n = 89, first trimester) and 298 with both. In women with both (n = 298) a pre-pregnancy weight one year prior to estimated conception date and first pregnancy weight, mean difference was very small (-1.4 lbs, p < -0.02). Pre-pregnancy weights are less influenced by pregnancy, e.g., hormones, fluid, weight gain, compared with first pregnancy weights. For these reasons and to maintain consistency in interpretation, pre-pregnancy weights up to one year prior to estimated conception date were used. A problem with use of weights one year before estimated conception date is the possibility that these women were pregnant and had given birth during the during this one year period. Thus, women were flagged if they had a pregnancy diagnoses or had delivered (n = 213) within the last year prior to estimated conception date and therefore they were excluded from pre-pregnancy weights. Estimated conception dates were calculated based on gestational age at delivery. The last measured height at a time point in adulthood was used for calculation of BMI. Pre-pregnancy BMI was calculated using pre-pregnancy weights as defined above and the last measured height available.

Pre-pregnancy weights and maternal heights were examined for extreme outliers. Detection of outliers was completed through observation of univariate distributions and descriptive analyses (mean, median, SD).

The National Research Council and Institute of Medicine (IOM) defines gestational weight gain (GWG) as “the amount of weight a pregnant woman gains between the time of conception and the onset of labor” 215. The recommended weight gain ranges based on pre-pregnancy BMI are: underweight (28 – 40 lbs), normal weight (25 – 35 lbs), overweight (15 – 25), obese (11 – 20 lbs). Often, there is lack of consistency in the time at which the last pregnancy weight is taken before the onset of labor. In addition, first and last pregnancy weights were mostly recorded in the paper charts during the selected years and were not adequately recorded electronically (36% of first pregnancy weights and 28% last pregnancy weights of the total number of linked records). This is probably due to the transition from paper charts to electronic medical records at KPH. In addition, the period of time during pregnancy at which the mother attended first and last pregnancy visits varied, in terms of trimester recorded. For example, there are ‘last’ pregnancy weights recorded in the second trimester which do not
provide a good indicator of actual GWG. Gestational weight gain information was also available from birth certificate information that was abstracted from KPH electronic/paper records. This was determined by the most recent weight during the pregnancy (to the date of recording) minus the starting weight from the first prenatal visit. There was more information provided through this variable than from the coded values in the EMR because of availability of chart-abstracted information supplementing the EMR.

Mother’s age at current pregnancy was described in years and determined at time of delivery. This variable was included as a precision variable. Mothers less than 16 years of age were excluded (2%) since peak attained height is usually reached by age 16 years by the average female as shown by the plateau in the CDC growth charts.216 During these earlier adolescent years, mothers are still growing and therefore calculated pre-pregnancy BMI would not be comparable with the remaining mothers.

Children born to women positive for gestational diabetes are born with a larger birth size147,217 and have an increased odds for child overweight.152 Diagnosis of GDM was determined by using ICD-9 coding for a diagnoses of GDM at delivery and was included in the model as a potential confounder. Birth order of the child was determined by parity (i.e., number of live births).

Maternal smoking during pregnancy is associated with a risk for a lower birth weight44,156 and also later child overweight.144,145,153-155 This is plausible through the mechanism of a lower birth weight and subsequent “catch-up” or rapid infant growth. Maternal smoking was included as a potential confounder. Maternal tobacco and alcohol use during pregnancy was coded as yes (vs. no) if they had smoked or drank alcohol at any point in pregnancy. A question from birth certificates asked “Tobacco use during pregnancy: yes or no”.

2.7 Missing Data

Intermittent missing data are common methodological problems in longitudinal studies. Well child visits are scheduled at specific ages during two years of life; however KPH members may not attend each visit or may not attend at the expected age. In addition, members join the health care system at different points in their lifetime. However, BMI data at age five years is expected to be relatively complete since children
registering for Kindergarten in the State of Hawai‘i usually require a physical examination by a physician. Comparisons of groups of subjects with and without birth size and growth data were completed to investigate selection bias and to determine whether missing data are “informative” or “ignorable” - specifically, comparisons of important predictor variables that are related to the outcome of interest (BMI at age five years), such as birth size, gestational age, age, sex, and ethnicity.

2.8 Final Study Sample

Figure 2.5 outlines the strategy used for determining the available study sample. After consideration of all main variables for analysis, a complete data set was available for a final sample of 894 children for Study Aim 1, 597 for Study Aim 2a, and 473 for Study Aim 2b, and 2c. (see Box A)
Figure 2.5. KPH EMR Sample of Children
2.10 Human Subjects Approval

This study was approved by the Kaiser Permanente Hawai‘i Institutional Review Board and the University of Hawai‘i Committee on Human Subjects.

2.11 Analytic Plan and Statistical Analyses

Descriptive statistics for dependent and independent variables were computed for continuous (mean, medians ± SD) and categorical (frequencies) variables. The main variables were BMI at age five years (dependent), birth weight (independent), gestational age, child’s age, sex, and ethnicity (covariates). Univariate and bivariate distributions of main variables were examined to identify outliers. Multiple regression model parameters were estimated to assess the association of a dependent variable with independent variables of interest, adjusting for covariates and potential confounders. The model building strategy included adding covariates and potential confounders to the core model that was derived from initial birth size analysis. The main core model included BMI at age five years as the dependent variable and birth weight adjusted for gestational age as an independent variable. For study aim 1, the covariates, child age, sex, and ethnicity, were added to the core model since they improve the precision of the model.

CORE MODEL: [Mean BMI at age 5 years = birth weight, gestational age, child age, sex, ethnicity]

After fitting the core model, the following covariates were screened by adding each variable one at a time: maternal height (in), pre-pregnancy weight (kg), BMI (kg/m²), age (years), education (years), smoking and alcohol during pregnancy (Y/N), GDM status (Y/N), parity (nulliparous, parous), and weight gain during pregnancy (lbs), and breast feeding (Y/N), and breastfeeding duration (months). Variables that modified the coefficient of birth weight by 10% \(116,219\) in the basic models and/or a p-value less than 0.2 \(220,221\) were included in subsequent multiple regression models. Statistical testing of linearity assumptions and tests for adequacy of the model were conducted by adding additional squared terms and cross products and testing if they were significant. Multivariate tests for differences in means between included and excluded
subpopulations were tested using logistic regression models. Demographics, main outcome and independent variables and explanatory variables were compared between the included and excluded samples to quantify the differences between the samples and their effect on study conclusions. Associations were considered non-significant if $p > 0.05$.

Change in infant growth as measured separately by weight, length, and weight-for-length was examined as a continuous variable and by the categorical variables of sex and race/ethnicity. Changes in weight and length were calculated as weight (kg) and length (cm) at age 22 to 24 months minus weight and length at age 2 to 4 months divided by difference in age in months. Weight/length is the ratio of relative weight in kg divided by length in cm. Change was calculated using the same age period as described for Study Aim 2. Infant weight (g/month), height (cm/month), and BMI (kg/m$^2$) change variables were added to the final core model from Study Aim 1 to examine the effect of infant growth on birth weight and BMI at age five years.

BMI is a moderate indicator of fatness in children$^{222}$ and, therefore, is more informative to study BMI as a continuous variable as opposed to using arbitrary intervals, assuming health risks increase with increasing body fatness. Linearity of BMI with age was assessed using its squared terms. BMI was examined as a continuous variable in statistical models.

Statistical analyses were conducted using the SAS Software program, Enterprise Guide 4.3.$^{223}$ A summary of the analysis steps for each aim is provided below.
AIM 1: Is Birth Size associated with Child BMI at age 5 years? 
Test the hypotheses: 
\[ H_0: \text{Birth weight is not associated with Child BMI at age 5 years}. \]
Dependent variable: BMI (kg/m²) at age 5 years
Independent variable: Birth Weight
Statistical Methods: Simple and Multiple Linear Regression

Example model building:
Dependent variable = Independent variable(s) + Precision Variables + Potential Confounders
1a) Mean BMI at age 5 years = birth weight (g)
Mean BMI at age 5 years = birth weight (g) + gestational age (weeks)
Mean BMI at age 5 years = birth weight (g) + gestational age (weeks) + child age (years) + sex + ethnicity
Mean BMI at age 5 years = birth weight (g) + gestational age (weeks) + child age (years) + sex + ethnicity + maternal variables

| COVARIATES |
|-----------------|-----------------|
| **Precision variables** | **Potential Confounders** |
| **Child variables** | Ethnicity (dummy, cat) |
| Sex (cat) | Maternal BMI (kg/m², cont) |
| Age (years, cont) | (Maternal Pre-pregnancy weight (kg, cont) |
| **Maternal variables** | Maternal Height (in, cont) |
| Gestational age (weeks, cont) | Maternal Smoking (Y/N, cat) |
| Maternal Age (years, cont) | GDM diagnoses during pregnancy (Y/N, cat) |
| Maternal Education (years, cont) | Breastfeeding (Y/N, cat) |
| Birth Order (0/ ≥ 1, cat) | |
| Breastfeeding Duration (months, cont) | |

Cont = continuous, Cat = categorical

Study Aim 1 SubAims
1b) Describe Birth Weight by Ethnicity and Sex
AIM 2: Is change in infant growth associated with Child BMI at age 5 years?

Test the hypothesis:

- **H₀: Change in weight** during infancy is not associated with child BMI at 5 years
- **H₀: Change in length** during infancy is not associated with child BMI at 5 years
- **H₀: Change in weight/length²** during infancy is not associated with child BMI at age 5 years

**Dependent variable:** BMI (kg/m²) at age 5 years

**Independent variable(s):** Change in weight, length, weight/length² during infancy

**Statistical Methods:** Simple and Multiple Linear Regression

### MODELS:

- **Calculated BMI (kg/m²) at age 5 years (continuous) = β₀ + β₁(infant growth, continuous)**
- **Infant growth (continuous) = θ₀ + θ₁(birth size, continuous)**

### Example Model Building:

- **Dependent variable = Independent variable(s) + Precision variables + Potential Confounders**

  2a) Mean BMI at age 5 years = birth weight (g) + gestational age (weeks) + child age + sex + ethnicity + maternal variables (dependent on results of Aim1) + change in weight (100 g/month)

### Other models to be tested:

- 2b) Mean BMI at age 5 years (cont) = change in length (cm/month)
- 2c) Mean BMI at age 5 years (cont) = change in weight/length² gain (kg/m²/month)

### COVARIATES (Dependent on Aim 1)

<table>
<thead>
<tr>
<th>Precision variables</th>
<th>Potential Confounders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child variables</strong></td>
<td><strong>Ethnicity (dummy, cat)</strong></td>
</tr>
<tr>
<td>Sex (cat)</td>
<td><strong>Maternal BMI (kg/m², cont)</strong></td>
</tr>
<tr>
<td>Age (years, cont)</td>
<td><strong>(Maternal Pre-pregnancy weight (kg, cont)</strong></td>
</tr>
<tr>
<td><strong>Maternal variables</strong></td>
<td><strong>Maternal Height (in, cont)</strong></td>
</tr>
<tr>
<td>Gestational age (weeks, cont)</td>
<td><strong>Maternal Smoking (Y/N, cat)</strong></td>
</tr>
<tr>
<td>Maternal Age (years, cont)</td>
<td><strong>GDM diagnoses during pregnancy (Y/N, cat)</strong></td>
</tr>
<tr>
<td>Maternal Education (years, cont)</td>
<td><strong>Breastfeeding (Y/N, cat)</strong></td>
</tr>
<tr>
<td>Birth Order (0/ ≥ 1, cat)</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding Duration (months, cont)</td>
<td></td>
</tr>
</tbody>
</table>

Cont = continuous, Cat = categorical
SubAims:
2d) Examine infant growth variables by sex and ethnicity
2e) Examine model 2a – c with binary outcome “overweight/not overweight” using logistic regression

AIM 3: Does change in infant growth mediate the relationship between birth weight and BMI at age 5 years?

Test the hypotheses:
H₀: The effect of birth weight on child BMI is not mediated through infant growth

Dependent variable: BMI (kg/m²) at age 5 years
Independent variable(s): Change in weight, length, weight/length² during infancy
Statistical Tests: Simple and Multiple Linear Regression

MODEL: Calculated BMI(kg/m²) at age 5 years (continuous) = β₀ + β₁ (infant Growth, continuous) + β₂ (Birth weight)

Calculated BMI(kg/m²) at age 5 years (continuous) = β₀ + β₁ (Birth weight) (model without infant growth)

Use core model and covariates used in Study Aim 1 and 2
AIM 4: Is the effect of Birth size on BMI at age 5 years modified by change in infant growth?

Test the hypothesis:

$H_0$: There is no interaction of infant growth and birth size and child BMI

MODEL: Calculated BMI (kg/m$^2$) at age 5y (continuous) = $\beta_0 + \beta_1$(infant Growth, continuous) + $\beta_2$ (Birth weight) + $\beta_3$ (Birth weight*infant growth)

Use core model and covariates used in Study Aim 1 and 2

Interaction Terms:
Birth weight and change in weight
Birth length and change in length
Birth weight/length$^2$ and change in weight/length$^2$
Figure 2.5 illustrates the sampling strategy for the study population. A total of 5,074 children met initial inclusion criteria, which included children born at KPH during the years 2004 – 2005 and current health plan members of KPH.

3.1 Core Model Results

3.1.1 Relative Role of Birth Weight, Birth Length, and Gestational Age in BMI at Age 5 Years

In preparation for Study Aim 1, birth size modeling was used to examine the association between BMI at age five years with birth weight, birth length, and gestational age. Birth size is described by weight in grams, length in centimeters, and weight/length$^p$ ($p =$ power of 0,1,2,3) and gestational age in weeks. To understand interrelationships further, correlation matrices were produced with birth size variables which provided preliminary information for model building. Various powers of birth size weight/length = $f$(weight/length$^p$) were tested as different functions of the ratio of weight/ length$^p$ to understand the relationship of weight to length at birth in relation to BMI at age five years. The best function or predictor of BMI in the model was used for future modeling.

Functions of Weight/Length$^p$ Tested:

Mean BMI at age 5y = $\beta_0 + \beta_1$ (birth weight/length$^p$) $P = 0,1,2,3$
Mean BMI at age 5y = $\beta_0 + \beta_1$ (birth weight) + $\beta_2$(birth length)
Mean BMI at age 5y = $\beta_0 + \beta_1$ (birth weight) + $\beta_2$(birth length) + $\beta_3$(birth weight/length)
Mean BMI at age 5y = $\beta_0 + \beta_1$ (birth weight) + $\beta_2$(birth length) + $\beta_3$(birth weight/length) + $\beta_4$(birth weight/length$^p$)

Gestational age is correlated with birth weight. Therefore a test was done to explore if adjusting for gestational age affected the regression of BMI (kg/m$^2$) at age five years on birth size. Models were adjusted for gestational age as appropriate.
Models Tested:

Mean BMI at age 5y = \( \beta_0 + \beta_1(\text{birth weight}) \)
Mean BMI at age 5y = \( \beta_0 + \beta_1(\text{birth weight}) + \beta_2(\text{gestational age}) \).

The overall sample was limited to those individuals who had clean data for birth weight, birth length, and gestational age and BMI at age five years (n = 1,729). In Table 3.1, bivariate analysis shows that both birth weight and birth length were positively associated with BMI at age five years. Addition of gestational age to the birth weight model strengthened the relationship of birth weight with BMI (\( \beta = 0.690 \) to 0.981) and was independently and inversely associated with BMI at age five years (\( \beta = -0.118, 95\% \text{ CI: -0.176 } - - 0.060, p = <0.0001) \). In model 4, birth weight adjusted for gestational age remains highly significant; therefore, gestational age needs to be included in the model. The test for interaction between birth weight and gestational age was not statistically significant. After adding birth length to the model with birth weight and gestational age, birth length was no longer a predictor of BMI and the interaction with birth weight and birth length was not statistically significant. Birth length was not included in subsequent models that examined the relationship of birth weight, gestational age, and BMI. In addition to absolute weight, functions of relative weight for length (weight for length, length\(^2\) and length\(^3\)), adjusted for gestational age, were tested. Coefficients of determination actually decreased when birth weight was adjusted for length in three different ways (Table 3.2). Thus, birth weight is an independent and stronger predictor of BMI at age five years than birth length or gestational age. A test for linearity was performed by adding squared terms to the model which were not significant. Thus, the birth size and gestational age modeling step resulted in the following core model:

\[
\text{Mean BMI at age 5y} = \beta_0 + \beta_1(\text{birth weight}) + \beta_2(\text{gestational age})
\]
Table 3.1. Birth Weight, Birth Length, Gestational Age and their Relative Contribution to BMI at Age 5 Years, β (95% CI) n = 1,729

<table>
<thead>
<tr>
<th></th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (kg)</td>
<td>0.690 (0.539 – 0.841)^</td>
<td></td>
<td>0.981 (0.774 – 1.19)^</td>
<td>0.993 (0.745 – 1.25)^</td>
<td></td>
</tr>
<tr>
<td>Birth Length (cm)</td>
<td></td>
<td>0.08 (0.056 – 0.112)^</td>
<td></td>
<td>-0.004 (-0.047 – 0.040)</td>
<td></td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td></td>
<td>0.070 (0.027 – 0.113)^</td>
<td>-0.118 (-0.176 – -0.060)^</td>
<td>-0.117 (-0.177 – -0.056)^</td>
<td></td>
</tr>
</tbody>
</table>

^p = <0.001, ^R^2 = 0.051, Interactions between birth weight with gestational age (p = 0.3318) and birth weight and birth length (p= 0.7762)

Table 3.2. Indices of Birth Weight for Birth Length adjusted for Gestational Age with BMI at Age 5 Years, β (95% CI) n = 1,729

<table>
<thead>
<tr>
<th></th>
<th>β ± SE</th>
<th>R^2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>0.690 ± 0.077*</td>
<td>0.051</td>
</tr>
<tr>
<td>Weight/Length</td>
<td>0.534 ± 0.061*</td>
<td>0.047</td>
</tr>
<tr>
<td>Weight/Length^2</td>
<td>0.198 ±0.030*</td>
<td>0.029</td>
</tr>
<tr>
<td>Weight/Length^3</td>
<td>0.048 ± 0.012*</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*p<0.001
Model building for Study Aim 1 was completed by adding other demographic and maternal factors that added precision to the model or were considered confounders of this relationship. Further analysis was completed on the cleaned data sample with the larger sample of cleaned birth weight and gestational age (n = 4,252) and not limited by available birth length (n = 2,946).

3.2 Study Aim 1

As depicted in Figure 2.5, children with cleaned birth weight and gestational age (n = 4,252) and a BMI measurement at age five years (n = 1,729) resulted in a sample of 1,729 children. Further addition of required covariates, including maternal variables resulted in a sample of 894 children. Descriptive data for this sample are provided in Tables 3.3 and 3.4. There were more male (53.6%) than female children. Most children were born close to term (38.7 weeks), on average. Mothers had a mean of 14 years of education and mean pre-pregnancy maternal BMI (26.5) was considered overweight by CDC BMI cut off points for adult criteria. The number of mothers who smoked (5.6%) or drank alcohol (1.6%) during pregnancy was low according to birth certificate information. Most children were breastfed for at least 18 months and were first born.

Table 3.3. Descriptive Statistics of Child Demographics (n = 894)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>415 (46.4)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70 (7.8)</td>
</tr>
<tr>
<td>Asian</td>
<td>264 (29.5)</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>330 (36.9)</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>181 (20.3)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (2.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>26 (2.9)</td>
</tr>
</tbody>
</table>

* Chinese (15.5%), Japanese (27.7%), Filipino (47.3%), Korean (1.9%), Asian Indian (0.8%), Vietnamese (1.5%), Thai (0.4%), Asian-NOS (4.9%)

* Persons race is recorded as combination of Native Hawaiian and any other race

* Guamanian (1.1%), Tahitian (1.1%), Samoan (14.4%), Tongan (1.1%), Pacific Islander – none other specified (82.3%)

* American Indian/Aleutian/Eskimo (17%), African American (26%), Other (57%)

* Race/Ethnicity information is missing
<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight (kg)</td>
<td>3.3 ± 0.6</td>
<td>0.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>38.7 ± 1.9</td>
<td>23.5</td>
<td>42.0</td>
</tr>
<tr>
<td><strong>Child at Age 5 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.9 ± 0.5</td>
<td>4.0</td>
<td>5.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.1 ± 1.8</td>
<td>11.7</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Maternal Variables and Infant Feeding</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy Weight (kg)</td>
<td>68.8 ± 18.7</td>
<td>33.1</td>
<td>161.9</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>29.5 ± 6.1</td>
<td>17.0</td>
<td>44.0</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)</td>
<td>26.5 ± 6.7</td>
<td>14.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Maternal Height (cm)</td>
<td>161.0 ± 7.1</td>
<td>131.6</td>
<td>190.5</td>
</tr>
<tr>
<td>Maternal Education (years)</td>
<td>14.0 ± 2.1</td>
<td>8.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Breastfeeding Duration (months)</td>
<td>18.0 ± 3.2</td>
<td>0.5</td>
<td>24.0</td>
</tr>
<tr>
<td>Maternal Weight Gain during Pregnancy (kg)</td>
<td>14.1 ± 5.7</td>
<td>4.1</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast-fed (Y/N)</td>
<td>888 (99.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Smoking (Y/N)</td>
<td>50 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Alcohol (Y/N)</td>
<td>14 (1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Order (&gt;1 live birth)</td>
<td>246 (27.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal GDMc (Yes, with diagnosis code)</td>
<td>100 (11.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a n = 888  b n = 461  c Gestational Diabetes Mellitus
Additional multiple regression models including maternal factors related to birth weight and later child BMI were estimated (Table 3.5) to explore the effect of these variables on the relationship between birth weight and BMI. Models were compared with the smaller sample size with breastfeeding duration information (n = 888). Due to minimal differences in regression coefficients (0.01 to 0.03 difference) the overall sample of n = 894 was retained for subsequent analysis.

Maternal pre-pregnancy weight, maternal BMI, maternal height, maternal age, maternal education, and maternal smoking met the criterion of p < 0.2 for inclusion into the core model. Maternal pre-pregnancy weight was positively associated ($\beta = 0.028$, 95% CI: 0.022 – 0.034) with BMI at age five years and decreased the effect of birth weight on BMI ($\beta = 0.926$ to 0.665). Maternal pre-pregnancy weight had a greater effect on infant birth weight than maternal BMI or height when included into the model, although maternal BMI still explained a higher proportion of the variability of BMI at age five years than other variables. Lower maternal education was associated with increased BMI at age five years ($\beta = -0.083$, p = 0.005). The effect of having been breastfed, breastfeeding duration, maternal alcohol consumption, maternal GDM status, maternal weight gain during pregnancy, and birth order on birth weight and BMI at age five were not significant (p >0.2) and were not included in subsequent models. These models explained only 7 – 8% of the variance. A sub-analysis was conducted on maternal weight gain since there was a much smaller sample that had this information (n = 439). An initial plausible range of weight gain of 11 to 65 lbs (5th to 95th percentile) was selected in our population based on distribution and after consulting current guidelines for GWG.\textsuperscript{215} However, it minimally affected the relationship of birth weight and BMI at age five years ($\beta = 0.926$ to $\beta = 0.838$). A sub-analysis of the effect of the larger range of weight gained (7 to 82 lbs, n = 461) was attempted; however, addition of another 18 values did not improve the model.
Table 3.5. Effect of Adding a Covariate on the Regression Coefficient of BMI at Age 5 Years on Birth Weight Core Model (n = 894)

<table>
<thead>
<tr>
<th>Covariates in the Model used to Adjust Birth Weight</th>
<th>Birth Weight (g)</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>Core Modela</td>
<td>0.926</td>
<td>0.662 – 1.192</td>
</tr>
<tr>
<td>Maternal Pre- pregnancy Wt (kg)b*</td>
<td>0.665</td>
<td>0.405 – 0.924</td>
</tr>
<tr>
<td>Maternal BMI (kg/m²)*</td>
<td>0.734</td>
<td>0.476 – 0.992</td>
</tr>
<tr>
<td>Maternal Weight Gain During Pregnancy (kg)c</td>
<td>0.838</td>
<td>0.461 – 1.216</td>
</tr>
<tr>
<td>Maternal Height (cm)*</td>
<td>0.868</td>
<td>0.599 – 1.136</td>
</tr>
<tr>
<td>Maternal GDM (Y/N)</td>
<td>0.917</td>
<td>0.651 – 1.184</td>
</tr>
<tr>
<td>Breast Fed (Y/N)</td>
<td>0.926</td>
<td>0.661 – 1.190</td>
</tr>
<tr>
<td>Breastfeeding Duration (months)</td>
<td>0.928</td>
<td>0.662 – 1.193</td>
</tr>
<tr>
<td>Birth Order (&gt; 1 live birth)</td>
<td>0.928</td>
<td>0.662 – 1.194</td>
</tr>
<tr>
<td>Maternal Alcohol during Pregnancy (Y/N)</td>
<td>0.928</td>
<td>0.663 – 1.192</td>
</tr>
<tr>
<td>Maternal Smoking during Pregnancy (Y/N)*</td>
<td>0.936</td>
<td>0.671 – 1.200</td>
</tr>
<tr>
<td>Maternal Education (years)*</td>
<td>0.939</td>
<td>0.675 – 1.202</td>
</tr>
<tr>
<td>Maternal Age at Pregnancy (years)*</td>
<td>0.957</td>
<td>0.689 – 1.224</td>
</tr>
</tbody>
</table>

* Variables included in subsequent modeling with p<0.02
aCore model = Birth weight, Gestational age, Child Age, Sex, Race/Ethnicity (Reference group = White), p<0.0001
bkilogram
clbs = pounds, n = 439
As explained in Chapter 2 (p.53), variables with significance levels < 0.2 were retained in the final model (Table 3.6). Pre-pregnancy weight, maternal age, maternal smoking, and maternal education were added one by one to the core model which improved the adjusted R² from 0.08 to 15.6%. Maternal BMI and maternal height with pre-pregnancy weight were also tested; however, pre-pregnancy weight (t = 8.83) was an overall better predictor than maternal BMI (t = 8.24) or maternal height (t = -0.16). Therefore pre-pregnancy weight was used in this model and had the most impact on the model R² (an increase from 0.08 to 0.15). Maternal education was no longer statistically significant after adding maternal age. The inclusion of all of these variables decreased the effect of birth weight on BMI (β = 0.926 to 0.707), justifying the need to adjust for these variables. Therefore this model (Table 3.6) became the final model for Study Aim 1. Higher birth weight and pre-pregnancy weight were both associated with higher BMI at age five years. Compared to Whites, Asian and Other Pacific Islander children had a higher BMI at age five years.

Mean birth weight was lowest among Asians (3.21 kg) followed by Other (3.20 kg), Native Hawaiian (3.32 kg), Unknown (3.34 kg), Other Pacific Islander (PI) (3.37 kg), and White (3.41 kg) (Figure 3.1). Asian children had a significantly lower birth weight compared with the Other PI children (p = 0.033). No other race/ethnic groups were significantly different. There was no statistical difference in birth weight between males (3.33 kg) and females (3.27 kg, p = 0.060, Figure 3.2). Study Aim 1 sample (n = 894) and the remaining sample (n = 3,358) were not statistically different (Wald X² = p < 0.054, Table 3.5). However, a few observed differences in race/ethnic groups were noted. Asian, Native Hawaiian, and Unknown race/ethnic groups had a >5% difference between samples. There were slightly more Asian and Native Hawaiian children in Study Aim 1 sample and more Unknown in the remaining sample.
Table 3.6. Regression of BMI at Age 5 Years on Birth Weight (FINAL MODEL*, n = 894)

<table>
<thead>
<tr>
<th>Variables</th>
<th>β</th>
<th>95% CI</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (kg)*</td>
<td>0.707</td>
<td>0.446 – 0.969</td>
<td>5.31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>-0.074</td>
<td>-0.150 – 0.001</td>
<td>-1.94</td>
<td>0.053</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.020</td>
<td>0.002 – 0.039</td>
<td>2.14</td>
<td>0.033</td>
</tr>
<tr>
<td>Female</td>
<td>-0.100</td>
<td>-0.320 – 0.120</td>
<td>-0.89</td>
<td>0.374</td>
</tr>
<tr>
<td>Asian</td>
<td>0.538</td>
<td>0.100 – 0.976</td>
<td>2.41</td>
<td>0.016</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>0.381</td>
<td>-0.059 – 0.821</td>
<td>1.70</td>
<td>0.090</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>0.623</td>
<td>0.153 – 1.094</td>
<td>2.60</td>
<td>0.010</td>
</tr>
<tr>
<td>Other Race/Ethnicity</td>
<td>0.290</td>
<td>-0.492 – 1.071</td>
<td>0.73</td>
<td>0.467</td>
</tr>
<tr>
<td>Unknown Race/Ethnicity</td>
<td>0.191</td>
<td>-0.568 – 0.949</td>
<td>0.49</td>
<td>0.622</td>
</tr>
<tr>
<td>Pre-pregnancy Weight (kg)</td>
<td>0.028</td>
<td>0.022 – 0.034</td>
<td>8.83</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Maternal Age at Pregnancy (years)</td>
<td>-0.014</td>
<td>-0.035 – 0.006</td>
<td>-1.36</td>
<td>0.175</td>
</tr>
<tr>
<td>Maternal Education (years)</td>
<td>-0.026</td>
<td>-0.087 – 0.035</td>
<td>-0.84</td>
<td>0.403</td>
</tr>
<tr>
<td>Maternal Smoking (Y/N)</td>
<td>0.390</td>
<td>-0.091 – 0.872</td>
<td>1.59</td>
<td>0.112</td>
</tr>
</tbody>
</table>

*Adjusted R² = 0.16, Reference Group = White
*kilogram
ANOVA: $F = 2.93$, $p < 0.008$, Adjusted for Sex

*p < 0.05

**Figure 3.1.** Birth Weight by Race/Ethnicity (n = 894)

ANOVA, $F = 3.55$, $p = 0.06$

**Figure 3.2.** Birth Weight by Sex (n = 894)
Table 3.7. Comparison of Demographics and Main Variables of Study Aim 1 Sample (n =894) with remaining Cleaned Birth Size Sample (n = 3358)

<table>
<thead>
<tr>
<th>Birth Characteristics</th>
<th>Study Aim 1 N = 894</th>
<th>N = 3358</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (kg)</td>
<td>3.3 ± 0.573</td>
<td>3.3 ± 0.601</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.7 ± 1.9</td>
<td>38.6 ± 2.1</td>
</tr>
<tr>
<td>Child Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>479 (53.6)</td>
<td>1671 (51.3)</td>
</tr>
<tr>
<td>Females</td>
<td>415 (46.4)</td>
<td>1589 (48.7)</td>
</tr>
<tr>
<td>Asian</td>
<td>264 (29.5)</td>
<td>744 (22.8)**</td>
</tr>
<tr>
<td>White</td>
<td>70 (7.8)</td>
<td>326 (10.0)**</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>330 (36.9)</td>
<td>829 (25.4)**</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>181 (20.3)</td>
<td>763 (23.4)**</td>
</tr>
<tr>
<td>Other Race/Ethnicity</td>
<td>23 (2.6)</td>
<td>100 (3.1)**</td>
</tr>
<tr>
<td>Unknown Race/Ethnicity</td>
<td>25 (2.6)</td>
<td>350 (10.7)**</td>
</tr>
<tr>
<td>Child BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI at age 5 years (kg/m^2)</td>
<td>16.2 ± 2.0 (n = 520)</td>
<td>16.3 ± 2.4 (n = 1079)</td>
</tr>
</tbody>
</table>

Overall Wald Chi Square, p < 0.054
* Total cleaned birth size sample, n = 4,252
** 98 missing, n = 3,260, total cleaned birth size sample, n = 4,154

3.2 Study Aim 2a – Change in Infant Weight

Among the 894 children included in Study Aim 1 who had both birth weight and gestational age measures, maternal information, and BMI calculated at age five years, 67% (n = 597) had a weight measured at three time points (2 to 4 months, 22 – 24 months, 4 to 6 years). In the Study Aim 2 sample, there were more males than females (53%) and a larger proportion of Asian, Native Hawaiian, and Other PI children than other race/ethnic groups (Table 3.6).

Mean birth weight, gestational age, child age, BMI at age five years, and maternal variables were similar to the means of the Study Aim 1 sample (Table 3.7). The mean infant weight gain was about 280 grams per month per child (114 – 498 g) for the infant growth period of 2.0 – 4.1 months to 22.4 – 24.4 months. Mean difference in months between measures was 20.4 (18.4 – 22.4 months). There were more weights and lengths measured at 2 and 24 months of the infant growth period being examined (Figure 3.3) which corresponds to the scheduled well child visits.
### Table 3.8. Descriptive Statistics of Child Demographics for Study Aim 2a (n = 597)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>283 (47.4)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47 (7.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>199 (33.3)</td>
</tr>
<tr>
<td>Native Hawaiian$^b$</td>
<td>216 (36.2)</td>
</tr>
<tr>
<td>Other Pacific Islander$^c$</td>
<td>110 (18.4)</td>
</tr>
<tr>
<td>Other$^d$</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Unknown$^e$</td>
<td>12 (2.0)</td>
</tr>
</tbody>
</table>

$^a$ Chinese (14.6%), Japanese (27.1%), Filipino (50.3%), Korean (1.5%), Asian Indian (1.0%), Vietnamese (1.5%), Asian-NOS (4.0 %)

$^b$ Persons race is recorded as combination of Native Hawaiian and any other race$^{20c}$ Guamanian(1.8%), Tahitian(1.8%), Samoan(16.4%), Tongan(1.8%), Pacific Islander – none other specified (78.2%)

$^c$ American Indian/Aleutian/Eskimo (7.7%), African American (38.5%), Other (53.8%)

$^d$ Race/Ethnicity information is missing

### Table 3.9. Descriptive Statistics of Birth Weight, Gestational Age, Infant Growth and BMI at Age 5 Years (n = 597)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth Weight (kg)$^a$</td>
<td>3.3 ± 0.6</td>
<td>0.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>38.6 ± 2.1</td>
<td>23.5</td>
<td>41.6</td>
</tr>
<tr>
<td><strong>Child at Age 5 Years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.4 ± 0.5</td>
<td>3.6</td>
<td>5.5</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>16.1 ± 1.8</td>
<td>11.7</td>
<td>23.5</td>
</tr>
<tr>
<td><strong>Infant Growth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Weight$^b$ (g/month)</td>
<td>285.4 ± 60.0</td>
<td>114.0</td>
<td>498.0</td>
</tr>
<tr>
<td>Difference in Age$^c$ (months)</td>
<td>20.5 ± 1.0</td>
<td>18.4</td>
<td>22.4</td>
</tr>
<tr>
<td>Maternal Variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy Weight (kg)</td>
<td>67.7 ± 18.2</td>
<td>36.3</td>
<td>161.9</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>29.5 ± 6.0</td>
<td>17.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Maternal Education (years)</td>
<td>14.0 ± 2.1</td>
<td>8.0</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Smoking (Y)</td>
<td>40 (6.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ kilograms

$^b$ Change in weight (100g/month) = Change in weight/Age at 22 to 24 month – Age at 2 to 4 months

$^c$ Age at 22 to 24 month – Age at 2 to 4 months
In the regression analysis of BMI on change in infant weight (Table 3.10), birth weight remained positively associated with BMI at age five years, after adjusting for the main independent variable of infant weight and covariates (age, child’s age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age and maternal education, and maternal smoking) in the model. A higher change in weight was also associated with a higher BMI at age five years, meaning that for every 100 g/month increase in weight, BMI increased by 1.0 kg/m² at age five years. Addition of the change in weight variable added 12% to the model variance (Adjusted $R^2 = 28\%$).

Asian ($\beta = 0.782$, 95% CI: 0.292 – 1.273), Other Pacific Islander ($\beta = 0.934$, 95% CI: 0.400 – 1.468), and Native Hawaiian ($\beta = 0.504$, 95% CI: 0.002 – 1.007) children had a higher BMI at age five years compared with White children adjusting for age, sex, pre-pregnancy weight, maternal education, maternal smoking, and rate of weight gain. Other and Unknown children were not significantly different from Whites. BMI at age five years was not significantly different among males and females. Change in weight was significantly different between race/ethnic groups (Figure 3.4); (ANOVA, $F = 2.68$, $p = 0.021$). White children had a significantly greater change in weight (313 g/month).
### Table 3.10. Analysis of Multiple Regression of BMI at Age 5 Years on Birth Weight and Change in Infant Weight\(^a\)
\((n = 597)\)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (kg)</td>
<td>0.688</td>
<td>0.374 – 1.002**</td>
<td>0.636</td>
<td>0.344 – 0.927**</td>
<td>-0.334</td>
<td>-1.368 – 0.700</td>
</tr>
<tr>
<td>Change in Infant Weight(^b) during Infant Period(^c) (100g/mo)</td>
<td>1.05</td>
<td>0.841 – 1.263**</td>
<td>-0.046</td>
<td>-1.190 – 1.097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction term: Birth Weight X Rate of Weight Gain</td>
<td></td>
<td></td>
<td>0.333</td>
<td>-0.008 – 0.673</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adjusted R\(^2\)**

| Variable  | 0.16 | 0.28 | 0.28 |

---

\(^a\)Models adjusted for gestational age, child age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age, maternal education, and maternal smoking

\(^b\)Change in weight (100g/month) = Change in weight/Age at 22 to 24 month – Age at 2 to 4 months

\(^c\)Infant period = 2 to 4 months to 22 to 24 months

** p\(<0.001**
Change in Weight = Between 2 to 24 months
ANOVA, F = 2.68, p= 0.02
*p<0.05

Figure 3.4. Change in Weight during the Infant Period by Ethnicity (n = 597)

than Asian (279 g/month, p = 0.006) and Native Hawaiian (283 g/month, p = 0.029) children. Change in weight was not significantly different among Other PI, Other, and Unknown race/ethnic groups compared with the other groups. However, sample sizes for the Other (n = 13) and Unknown groups (n = 12) were small and it is possible that there was not enough power to detect a moderate difference.

Also, after plotting weight over time, Pacific Islanders had a different trajectory after the first two years of life compared with other groups (Figure 3.5). Change in weight during the infant period was not statistically different between males (286 g/month) and females (284 g/month). Weight gain from birth to age five years was similar for males and females with males at a slightly higher trajectory from 2 to 4 months to 22 to 24 months than females.

Comparisons were made among the Study Aim 2a sample (n = 597) with children who did not have weight and length measures within the specified time period (n = 3625, Table 3.9). The overall Wald X² was not significant, indicating that statistical differences were not detectable between study samples. There were minimal differences
in birth weight, gestational age, sex, and BMI at age five years between samples. The Study Aim 2a sample had more Asian and Native Hawaiian children, and fewer Other Pacific Islander children and Unknown race/ethnicity group which may imply that these groups may attend fewer well child visits.

Figure 3.5. Change in Weight\(^a\) from Birth to Age Five Years by Race/Ethnicity (n = 597)

\(^a\)Change in Weight = Between 2 to 24 months
Other PI = Other Pacific Islanders
Change in Weight = Between 2 to 24 months
ANOVA, $F = 0.13$, $p = 0.720$

Figure 3.6. Change in Weight$^a$ during the Infant Period by Sex (n = 597)

Figure 3.7. Change in Weight$^a$ from Birth to Age 5 Years by Sex (n = 597)
Table 3.11. Comparison of Demographics and Main Variables of Study Aim 2a Sample (n = 597) with Sample without Weights and Lengths within Specified Time Periods (n = 3625)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N = 597</th>
<th>N = 3,625</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>38.6 ± 2.1</td>
<td>38.6 ± 2.1</td>
</tr>
<tr>
<td><strong>Child Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>314 (52.6)</td>
<td>1828 (51.8)*</td>
</tr>
<tr>
<td>Females</td>
<td>283 (47.4)</td>
<td>1699 (48.2)*</td>
</tr>
<tr>
<td>Asian</td>
<td>199 (33.3)</td>
<td>803 (22.8)*</td>
</tr>
<tr>
<td>White</td>
<td>47 (7.9)</td>
<td>348 (9.9)*</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>216 (36.2)</td>
<td>940 (26.7)*</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>110 (18.4)</td>
<td>825 (23.4)*</td>
</tr>
<tr>
<td>Other Race/Ethnicity</td>
<td>13 (2.2)</td>
<td>110 (3.1)*</td>
</tr>
<tr>
<td>Unknown Race/Ethnicity</td>
<td>11 (1.8)</td>
<td>359 (10.2)*</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>16.2 ± 2.1 (n = 200)</td>
<td>16.2 ± 2.0 (n = 882)</td>
</tr>
</tbody>
</table>

Overall Wald Chi Square, p<0.104
* Total cleaned birth size sample, n = 4,222
** 98 missing, n = 3,527, total cleaned birth size sample, n = 4,124

3.3 Study Aims 2b and 2c

The final sample to examine the association of change in length between 2 and 24 months of age and BMI consisted of 473 children. Length measures were less available than weight measures, therefore limiting the sample to those with both measures. Descriptive statistics for this sample are reported in Tables 3.12 and 3.13.

There were similar proportions of males and females, and numbers for the Other and Unknown ethnic groups were small. Birth size, child age and BMI, and maternal values were similar with this final sample of n = 473. Average rate of length gain was 1.2 cm/month and BMI gain was -0.04 kg/m²/month over a 20 month duration.

Change in length was positively associated with BMI at age five years (Table 3.14). A 1 cm/month increase in length was associated with a 1.6 kg/m² increase in BMI at age five years. This change in length did not vary by race/ethnicity (Figure 3.8, F = 1.25, p = 0.284) and initial plots of length gain (Figure 3.9) demonstrates that a similar pattern was followed by all race/ethnic groups. However a visible separation was noted after 24 months with the Other and Other PI children at the top of all other race/ethnic
plots. Change in length and pattern of length/height growth was not different between males (1.22 cm/month) and females (1.25 cm/month, p = 0.105) (Figures 3.10 and 3.11).

Table 3.12. Descriptive Statistics of Child Demographics of Children in the Final Sample (n = 473)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>233 (49.3)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>40 (8.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>172 (36.4)</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>152 (32.1)</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>89 (18.8)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (2.5)</td>
</tr>
</tbody>
</table>

* Chinese (15.1%), Japanese (28.5%), Filipino (48.3%), Korean (1.7%), Asian Indian (1.2%), Vietnamese (1.2%), Asian-NOS (4.1%)

*b* Persons race is recorded as combination of Native Hawaiian and any other race208

*c* Guamanian(1.1%), Tahitian(1.1%), Samoan(16.9%), Tongan(1.1%), Pacific Islander – none other specified (79.8%)

*d* American Indian/Aleutian/Eskimo (12.5%), African American (37.5%), Other (50%)

*e* Race/Ethnicity information is missing
Table 3.13. Descriptive Statistics for Birth Weight, Gestational Age, Change in Length\(^a\) and BMI\(^b\) and BMI at Age 5 Years (n = 473)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Size</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.3 ± 0.6</td>
<td>1.0</td>
<td>4.7</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>38.7 ± 2.0</td>
<td>27.0</td>
<td>41.6</td>
</tr>
<tr>
<td><strong>Child at Age 5 years</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>4.4 ± 0.5</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>16.1 ± 1.8</td>
<td>11.7</td>
<td>25.0</td>
</tr>
<tr>
<td><strong>Infant Growth</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in Length (cm/month)(^a)</td>
<td>1.2 ± 0.2</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Change in BMI (kg/m(^2)/month)(^b)</td>
<td>-0.04 ± 0.1</td>
<td>-0.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Difference in Age (month)(^c)</td>
<td>20.7 ± 1.0</td>
<td>18.4</td>
<td>22.4</td>
</tr>
<tr>
<td><strong>Maternal Variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy weight (kg)</td>
<td>67.6 ± 17.9</td>
<td>38.6</td>
<td>161.9</td>
</tr>
<tr>
<td>Maternal Age (years)</td>
<td>30.1 ± 5.9</td>
<td>17.0</td>
<td>42.0</td>
</tr>
<tr>
<td>Maternal Education (years)</td>
<td>14.0 ± 2.1</td>
<td>8.0</td>
<td>17.0</td>
</tr>
<tr>
<td>Maternal Smoking (Y/N)</td>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal Smoking (Y/N)</td>
<td>31 (6.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Change in Length (cm/month) = Change in length / Age at 22 to 24 months – Age at 2 to 4 months

\(^b\)Change in BMI (kg/m\(^2\)/month) = Change in BMI/Age at 22 to 24 months – Age at 2 to 4 months

\(^c\)Age at 22 to 24 months – Age at 2 to 4 months
Table 3.14. Analysis of Multiple Regression of BMI at Age 5 Years on Birth Weight and Change in Length (n = 473)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \beta )</td>
<td>95% CI</td>
<td>( \beta )</td>
<td>95% CI</td>
<td>( \beta )</td>
<td>95% CI</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>0.816</td>
<td>0.459 – 1.173***</td>
<td>0.840</td>
<td>0.487 – 1.193***</td>
<td>0.186</td>
<td>-1.788 – 2.160</td>
</tr>
<tr>
<td>Change in length(^{b}) during infant period(^{c}) (cm/month)</td>
<td>1.583</td>
<td>0.668 – 2.498***</td>
<td></td>
<td>-0.082</td>
<td></td>
<td>-5.113 – 4.950</td>
</tr>
<tr>
<td>Interaction Term: Birth weight X Change in length</td>
<td></td>
<td></td>
<td></td>
<td>0.511</td>
<td></td>
<td>-1.007 – 2.029</td>
</tr>
<tr>
<td>Adjusted R(^2)</td>
<td>0.15</td>
<td></td>
<td>0.17</td>
<td></td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Models adjusted for gestational age, child age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age, maternal education, maternal smoking  
\(^b\)Change in Length (cm/month) = Change in length / Age at 22 to 24 months – Age at 2 to 4 months  
\(^c\)Infant period = 2 to 4 months to 22 to 24 months  
**p<0.001**
*Change in Length = Between 2 to 24 months
ANOVA, F = 1.72, p = 0.129

**Figure 3.8.** Change in Length* during the Infant Period by Race/Ethnicity (n = 473)

*Change in Length = Between 2 to 24 months
Other PI = Other Pacific Islander

**Figure 3.9.** Change in Length* from Birth to 5 Years of Age by Race/Ethnicity (n = 473)
Change in Length = Between 2 to 24 months
ANOVA, F = 2.95, p = 0.087

Figure 3.10. Change in Length\textsuperscript{a} during the Infant Period by Sex (n = 473)

Figure 3.11. Change in Length\textsuperscript{a} from Birth to 5 Years of Age by Sex (n = 473)
Change in BMI between 2 and 24 months was not associated with BMI at age five years (Table 3.15) and did not vary by race/ethnicity (range = 0.02 – 0.05 kg/m², Figure 3.12) or by sex (p = 0.8078, Figure 3.11). BMI plotted over time also shows initial difference from birth to about one year of age and where there is a decline; and, at two years of age, race/ethnic difference of patterns of growth visually emerge (Figure 3.13).

There were no statistical differences in BMI between males and females (Figure 3.14). BMI plotted over time by sex varied slightly at the 2 to 4 month BMI and became equal at age five years (Figure 3.15). Comparisons were made between the Study Aim 2b and 2c samples (n = 473) with children who did not have length measures in Study Aim 2a (n = 413, Table 3.16). The overall Wald $\chi^2$ was significant (p<0.000), however differences were between race/ethnic groups but not the main independent variables (birth weight and gestational age) and BMI at age five years. Study Aim 2b and 2c samples had more Asian (36.4% vs. 21.9%) and White (8.5% vs. 7.1%) and fewer Native Hawaiian (32.1% vs 42.3), Other Pacific Islander (18.8% vs. 21.9%, Other (1.7% vs. 3.6%) and Unknown (2.3% vs. 3.3%) children compared with the remaining sample.

Children with early disease conditions and congenital anomalies present at birth may influence birth size, infant growth, and later BMI. Logistic regression was used to compare differences in the main variables between those with and without congenital anomalies for Study Aim 1 (n = 87 of 894). Gestational age (Wald $\chi^2$, 9.29, p = 0.002) was slightly lower (38.0 ± 3.4 weeks) in the group with congenital anomalies compared to those without (38.7 ± 1.7 weeks).

In the KPH sample, 10% (Study Aim 1, 89 of 894) met the preterm birth definition. Sub-analysis using logistic regression was conducted to test if preterm births influenced the results and no differences were noted. Since there were no major differences in the results of comparisons with and without congenital anomaly and preterm subgroups, these children were retained for the purposes of this study and in the interest of describing the overall KPH child population five years of age. For further understanding of these relationships, later sub-analyses will be considered.
Table 3.15. Analysis of Multiple Regression of BMI at Age Five Years on Birth Weight and Change in BMI (n = 473)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Model 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
<td>β</td>
<td>95% CI</td>
</tr>
<tr>
<td>Birth BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.817</td>
<td>0.461 – 1.173&lt;sup&gt;***&lt;/sup&gt;</td>
<td>0.821</td>
<td>0.463 – 1.178&lt;sup&gt;***&lt;/sup&gt;</td>
<td>0.850</td>
<td>0.465 – 1.235&lt;sup&gt;***&lt;/sup&gt;</td>
</tr>
<tr>
<td>Change in BMI&lt;sup&gt;b&lt;/sup&gt; during infant period (kg/m&lt;sup&gt;2&lt;/sup&gt;/month)</td>
<td>0.400</td>
<td>-1.293 – 2.093</td>
<td></td>
<td></td>
<td>-1.759</td>
<td>-12.336 – 8.819</td>
</tr>
<tr>
<td>Interaction Term: Birth Weight X Change in BMI</td>
<td></td>
<td></td>
<td>0.669</td>
<td>-2.569 – 3.908</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted R&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.15</td>
<td></td>
<td>0.15</td>
<td></td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Models adjusted for gestational age, child age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age, maternal education, maternal smoking

<sup>b</sup>Change in BMI (kg/m<sup>2</sup>/month) = Change in BMI/Age at 22 to 24 months – Age at 2 to 4 months

<sup>c</sup>Infant period = 2 to 4 months to 22 to 24 months

*** p<0.001
ANOVA, $F = 1.03$, $p = 0.401$

**Figure 3.12.** Change in BMI during the Infant Period by Race/Ethnicity (N = 473)

**Figure 3.13.** Change in BMI from Birth to Age 5 Years by Race/Ethnicity (n = 473)
ANOVA, $F = 0.06, p = 0.808$

**Figure 3.14.** Change in BMI Differences by Sex ($n = 473$)

**Figure 3.15.** Change in BMI from Birth to Age 5 Years by Sex ($n = 473$)
Table 3.16. Comparison of Child Demographics and Main Variables of Study Aim 2b Sample (n = 473) with Sample* without Growth Data within Specified Time Periods (n = 421)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n = 473</th>
<th>n = 421</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birth Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>38.7 ± 1.8</td>
<td>38.6 ± 2.1</td>
</tr>
<tr>
<td><strong>Child Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>240 (50.7)</td>
<td>239 (56.8)</td>
</tr>
<tr>
<td>Females</td>
<td>233 (49.3)</td>
<td>182 (43.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>172 (36.4)</td>
<td>92 (21.9)</td>
</tr>
<tr>
<td>White</td>
<td>40 (8.5)</td>
<td>30 (7.1)</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>152 (32.1)</td>
<td>178 (42.3)</td>
</tr>
<tr>
<td>Other Pacific Islander</td>
<td>89 (18.8)</td>
<td>92 (21.9)</td>
</tr>
<tr>
<td>Other Race/Ethnicity</td>
<td>8 (1.7)</td>
<td>15 (3.6)</td>
</tr>
<tr>
<td>Unknown Race/Ethnicity</td>
<td>11 (2.3)</td>
<td>14 (3.3)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>16.0 ± 1.8</td>
<td>16.1 ± 1.8</td>
</tr>
</tbody>
</table>

Overall Wald Chi Square, p<0.000
* Total Sample from Aim 1, n = 894

3.4 Study Aim 3 and 4 – Mediation or Moderation by Infant Growth

For Study Aim 3, change in infant weight was not significantly associated with birth weight (p = 0.385) and including it in the regression model changed the regression coefficient for birth weight by only 7.6%. Similarly, change in infant length and change in infant BMI changed the regression coefficient of birth weight by 2.9% and 0.5% respectively. There was no evidence of mediation of the relationship of birth weight and BMI at age five years by infant growth. For Study Aim 4, tests of significance for the interaction between birth weight and change in weight (p = 0.055), change in length (p = 0.509), and change in BMI (p = 0.685) were not statistically significant.
Adjusted for gestational age, child age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age, maternal education, maternal smoking

*** p<0.001

Figure 3.16. Mediation of Change in Infant Weight on Birth Weight and Child BMI at Age 5 Years Relationship

Figure 3.17. Mediation of Change in Infant Length on Birth Weight and Child BMI at Age 5 Years Relationship
Adjusted for gestational age, child age, child ethnicity, child sex, maternal pre-pregnancy weight, maternal age, maternal education, maternal smoking

*** p<0.001

**Figure 3.18.** Mediation of Change in Infant BMI on Birth Weight and Child BMI at Age 5 Years Relationship
CHAPTER 4. DISCUSSION

This study demonstrates that a higher birth weight and greater change in weight and length during infancy, but not change in BMI during infancy, are associated with a higher BMI at age five years. Furthermore, the role of underlying factors that influence these relationships such as maternal factors, infant feeding, timing and amount of gain and variation by race/ethnic group during the first five years are discussed.

4.1 Higher Birth Weight, Higher BMI at Age 5 Years

Birth weight is an independent and stronger predictor of BMI at age five years than birth length or gestational age. In addition to absolute weight, functions of relative weight for length (weight for length, length$^2$ and length$^3$), adjusted for gestational age, did not account for additional variance as compared to previous birth weight models.

A higher birth weight was associated with a higher BMI at age approximately five years, adjusting for gestational age, sex, child’s age, race/ethnicity, maternal pre-pregnancy weight, maternal age at pregnancy, maternal smoking, and maternal education. This study validates the results of previous studies, in a multiethnic population, adjusting for gestational age, and other maternal factors previously not considered or available. Other factors that were in the causal pathway of birth weight and BMI at age five years, such as infant growth and feeding, were further explored.

4.2 Higher Change in Weight and Length, Higher BMI at Age 5 Years

A 100 g/month increase in weight during the first two years (gain at the 50th percentile from 2 to 24 months) was associated with a 1 kg/m$^2$ increase in BMI. The average duration of time measured for the infant growth period (2.04 – 4.07 months to 22.4 – 24.4 months) ranged from 18.4 – 22.4 total months. According to the Nelson’s Textbook of Pediatrics, children are expected to gain weight; and, approximate daily weight gain varies by the age of the child reference. Figure 4.1 provides a visual depiction of expected weight gain velocity (kg/year) that occurs from birth to adolescence illustrated by Tanner and Whitehouse. Most infant weight gain occurs in the first year
Figure 4.1 KPH Weight Velocity Plot²²⁶ from 1 to 5 Years of Age
year (e.g., 30 g/day from 0 to 3 months, 12 g/day from 9 to 12 months) then drops to 8 g/day in years 1 - 3 and 6 g/day from years 4 – 6. If extrapolated over a 24 month period, growth reference children would gain about 410 g/month (9.8 kg/year), average rate of weight gain in the KPH sample would be 388 g/month (9.3 kg/year), high rate of weight gain would be 571 g/month (13.7 kg/year), and low rate of weight gain would be 237 g/month (5.7 kg/year). However, comparability of the KPH rate of weight gain with the growth reference is questionable since the reference calculated values of daily and monthly growth are based on data from the Fels Longitudinal Study of primarily White middle-class children who were predominantly formula fed. Nonetheless, actual weight gain per month in KPH White children was 313 g/month, similar to the Fels growth reference of 370 g/month. For the actual present study sample period of 21 months, the mean weight gain was about 280 g/month.

Very few studies have examined rate of infant weight gain as a continuous variable. However, a continuous variable would be representative of the biology of growth and can provide a basis for clinical application. Stettler et al. examined infant weight gain in g/month and reported that for every 100 g/month increase between birth and four months, risk for child obesity at seven years, or later, increased by 17% after adjustment for weight at one year. In comparison with the current study time period (2 to 24 months), a sustained increase of 100 g/month weight may increase risk for later overweight, since this is over a longer period of time.

Another study completed with pediatric health maintenance records (n = 129) examined growth data as a continuous variable. Using receiver operating characteristic (ROC) curve analysis, Gungor et al. determined a category of “risky” infant weight gain, which was selected after examining sensitivity and specificity in a period where child overweight risk was best predicted. Infants defined as “at-risk” gained 8.2 and up to 10.2 kg between the ages of 0 to 24 months. Interestingly, 31.4% of at-risk children became overweight; and the rest were defined as “resilient” (68.6%). The child overweight prevalence in the cohort was 24.8% and increased to 31.4% in at-risk infants. Characteristics of resilient children included lower weight gain during this period, parents who were more educated, being exclusively breastfed for six months or longer and introduction of solid foods at a later time. This study highlights the
importance of other behavioral factors that predict rate of growth during this time period
that are crucial to later development (after infancy). The authors state that 8.2 kg is
certainly not considered rapid in two years since there are infants who would still track
on a centile line at this weight. However, they still find it appropriate to define this
threshold as “risky” growth. In addition, they justify that the high prevalence of
overweight in their study indicates that growth does not have to be rapid to be risky and
another recent study supports this notion that “normal infant growth is not without
risk”.229 This study was limited in that it had a relatively small sample (n = 129).

Using similar methods, Toshke et al. assigned risk for child overweight using the
best combined sensitivity and specificity which was at 9.8 kg (higher than the 8.2 kg
threshold).109 One difference of both of these studies compared to the present study is
whether the ROC method would provide the same threshold amount of weight gain and
optimal screening interval during childhood for a multiethnic population. This study’s
population had a mean total of about 5.9 kg gain (280 g/month x average of 21 months)
in the first 21 months. Over an estimated equivalent period of 24 months, KPH children
on the high end of the range grew approximately about 13.7 kg or 3.9 to 5.5 kg more than
the above 8.2 kg or 9.8 kg thresholds.109, 228 In comparison with a sample of French
children (n = 1,582), KPH children grew at a faster rate of 388 g/month compared with
285 g/month over the first two years of life.230 Risk for overweight at ages 7 to 9 years
was associated with 246g/month weight gain in boys (OR for 100 g/mo = 2.06, 95% CI:
1.22 - 3.48) and weight at one year (9.4 kg) in girls (OR for 1 kg = 2.24, 95% CI: 1.37 -
3.66) average variation in monthly weight gain (-13.8 g in boys and – 11.8 g in girls) or
change in velocity slope (OR for 1 g = 1.13, 95% CI: 1.04 - 1.22).230 These studies
provide reference for comparison and understanding infant growth in terms of weight
gain in grams per month, race/ethnicity, and sex differences in study populations.

In the current study, a higher length gain during the infant period was associated
with a higher BMI at age five years. A similar finding was noted from birth up to 1 year
of age in a study of Mexican children where change in length-for-age z score was
positively associated with BMI z-score at age 4 to 6 years (p < 0.01).31 Length is a part
of the BMI measure and children continue to gain in length based on their genetic
potential during these first two years, even though weight and length gain may decelerate during the 2nd year.

4.3 Change in BMI in the first 2 years was not associated with BMI at age 5 years

The BMI measure consists of weight adjusted for length. This measure illustrates the natural deceleration or ‘slowing down’ of growth that occurs during the second year of life; however, if observed as separate measures of infant weight and length gain, the gradual increase indicates continuation of normal growth.

4.4 Effect of Birth Weight on BMI at age 5 years is not mediated by Infant Growth in the First Two Years

Change in infant weight, length, or BMI did not play a role as mediator for the effect of birth weight and BMI at age five years. It has also been hypothesized that birth weight is a mediator itself in the pathway of maternal factors and later child overweight.

In previous studies, levels of birth weight [e.g., small-for-gestational- age (SGA) or appropriate-for-gestational-age (AGA)] and infant weight gain modified the effect of birth weight on BMI at age five years. In this study, the interaction terms that included birth weight and change in infant weight gain, length, and BMI were tested; however, for three separate tests for interaction, a Bonferroni adjustment would require a p-value of $0.05/3 = 0.0167$. The smallest of the three p-values was 0.058, which is not significant.

It is also possible that an effect of different levels of birth weight or infant growth on BMI at age five years may not be detectable due to a canceling out of effects due to differences by race/ethnicity. Whites and Other PI children were born with larger birth weights than other groups; however, Whites grew much faster during the infant period, whereas the Other PI group seems to pick up their growth rate after two years.

4.5 Birth Weight, Change in Infant Weight, and BMI at Age 5 Years vary by Race/Ethnicity

The effect of biological differences that exist between race/ethnic groups and the burden of clinical measurement are evident. A recent study reported that South Asian infants in Canada were being misclassified as underweight at birth or small for gestational age, which then facilitated further tests and possibly unnecessary stress for the
infant and parents.\textsuperscript{231} The authors have since developed birth weight curves for the maternal world region.\textsuperscript{232} Another study done at KPH included more screen positives in genetic sonograms due to shorter long bone measures in non-white ethnic groups.\textsuperscript{233}

Birth weight varied by race/ethnicity between the Asian and Other Pacific Islanders, 3.21 vs. 3.37 kg, \( p = 0.03 \). Change in infant weight reflected a similar pattern of birth weight differences in race/ethnic groups (Figure 4.2). White children had a higher mean birth weight and change in infant weight compared to Asian and Other PI children.

Other PI and White children had higher birth weights than other race/ethnic groups. However, change in infant weight was higher in White children than Other PI. It appears that Other PI children experience a slower change in infant weight in the first two years and have more weight gain in the following three years after the infant period, compared with other race/ethnic groups (Figure 4.3). In another study, Rush and colleagues reported that Pacific Islander children were born heavy, had faster weight gain over four years, and faster height gain between two and four years.\textsuperscript{234}

\textbf{Figure 4.2.} Birth Weight and Change in Weight shared a similar pattern by Race/Ethnicity
**Figure 4.3.** Change in Weight varied by Race/Ethnicity and Age in Months

Exploration of BMI plotted over time provides a visual presentation of race/ethnic differences and timing of these differences (Figure 4.4). Other PI and White children appear to experience a slower BMI deceleration with age compared with Asian, Native Hawaiian, Other, Unknown, which corresponds with the reported change in BMI values.

**Figure 4.4.** Visual Plots showing Different Trajectories by Race/Ethnicity
noted in Figure 3.12 (Other PI, -0.02 kg/m$^2$, White, -0.03 kg/m$^2$, Asian, Other, Unknown -0.04 kg/m$^2$, Native Hawaiian -0.05 kg/m$^2$). From two to four months of age there is a notable difference in deceleration patterns of BMI between race/ethnic groups. White children decrease at a slower rate until about two years of age and then decrease to a lower BMI compared with all race/ethnic groups at age five, whereas the Other PI children markedly increase in BMI from 2 to 5 years.

Asian, Native Hawaiian, and Unknown children also decreased or maintained their BMI from 2 to 5 years. The Other race/ethnic group mimics the pattern of Other PI but ends at a lower BMI at age five years. Other Pacific Islanders had a significantly higher BMI at age five years compared with Asian and White children (16.5 vs. 15.9 kg/m$^2$, $p = 0.005$ and 15.5 kg/m$^2$, $p = 0.002$). Native Hawaiian children were also significantly higher in BMI than White children (16.2 and 15.5 kg/m$^2$, $p = 0.044$).

The “adiposity rebound” period, is a term coined by Rolland-Cachera,$^{235}$ describes the period when there is a decrease in BMI until it reaches its nadir and then starts to increase again. Studies have described the association of an early adiposity rebound with later overweight due to children gaining more weight over a longer period. After about one year of age, BMI decreases through the preschool years until it reaches its nadir, which usually occurs between 5 to 7 years of age.$^{235}$ It is interesting to note that the “adiposity rebound” period appears to be occurring earlier for the Other PI and Other groups as designated by the circle around age two years. The remaining race/ethnic groups seem to experience their adiposity rebound at the usual period of ages 4 up to 7 years.

It has also been demonstrated that the earlier adiposity rebound results in a gain in fat mass versus lean mass in girls.$^{236}$ Type of body mass (lean and fat mass) that is gained by sex and race/ethnic group may also vary dependent on timing of adiposity rebound. The adiposity rebound period was not an aim of this study due to the need to have more growth points past five years of age to identify the age adequately at which this occurs. The longitudinal plot of BMI provides a visual explanation for differences between race/ethnic groups that require further study.

The interplay of biology and environmental or lifestyle factors after birth may influence future growth trajectories. The growth trajectory of the first two years may be
influenced by prenatal experience and enhanced by exposure to first foods (e.g., breastmilk, formula) and transition to solids/juices/dairy milk and development of food preferences that assist in reaching the genetic potential. The growth trajectory after two years of age is then coupled with continued exposure to new foods (e.g., introduction to table foods) and new environments, such as preschool, that introduce an added layer of factors that influence behavior.

In the Feeding Infants and Toddlers Study (FITS) a large percentage of calories from table foods were consumed in the form of desserts / daily candy and French fries, which was the most reported vegetable at age 18 to 24 months. Family structure (older siblings, single parent) and lifestyle “cast a mold” for these exposures. For example, busy lifestyles that include after school activities call for more fast food consumption on school nights, thus increasing exposure to easy, soft finger foods such as french fries.

Cultural factors may influence food introduction and selection, which would impact food preferences in the next three years, up to age five years. Mothers’ food selection and preferences are also influential at this point. In particular, mothers who are already overweight may have established unhealthy eating and physical activity habits that are passed to her child.

### 4.6 Maternal Pre-Pregnancy Weight and Child BMI

A higher pre-pregnancy weight was associated with a higher BMI at age five years and was a confounder of the relationship of birth weight and BMI. Pre-pregnancy weight was a better predictor of child BMI compared with maternal height and BMI. Younger maternal age was associated with higher BMI at age five years. However, when adjusted for maternal education the effect was attenuated. Maternal nutrition has also been related to maternal obesity during pregnancy which is intuitive because there could be a connection between maternal feeding habits and formation of infant to child feeding habits. Indicators of maternal lifestyle factors, starting with breastfeeding exclusively, financial situation, work environment, and education, are also key to formation of healthy habits of mother and infant.

Adjusted for gestational age, absolute mass of the infant at birth (birth weight) was more highly associated with child’s BMI at age five years, than BMI at birth or other
measures of relative weight (weight/length, weight/length^2, weight/length^3). In addition, maternal pre-pregnancy weight (r = 0.29) had a higher correlation with child’s BMI at age five years than maternal BMI (r = 0.27).

Maternal weight gain would intuitively be a possible mediator in the relationship of pre-pregnancy weight and BMI at age five years which is also indicative of the importance of maternal weight. However, maternal weight gain was not a predictor of child BMI at age five years in this study. It is also plausible that the association of maternal pre-pregnancy weight and child BMI at age five years is an indicator of the influences of a shared environment and dietary habits of the mother that supports development of later overweight in children of school-age.\(^{239}\)

### 4.7 Clinical applications

Previous studies have defined growth as rapid when it reaches > 0.67 SD, which is a measure of the SD between the percentiles of the United Kingdom (UK) growth chart. It can be argued that the reference UK growth chart is different from the current CDC/WHO growth chart, and therefore the > 0.67 SD may not be a good marker for crossing percentiles in the US. Clinicians typically use upward crossing of two or more percentiles for weight-for-length or BMI as an indicator of risk for later child obesity. In the interest of clinical application, a longitudinal study conducted at another multi-site clinical practice examined the growth of children who crossed upwards of two or more weight-for-length percentiles in the first 24 months. These children had two times the risk of developing obesity at age five years (OR = 2.08, 95% CI: 1.84 – 2.34).\(^{240}\) Obesity prevalence at five years was highest (32.9%) in children who crossed percentiles in the first six months compared with 6 and 12 months (29.7%), 12 to 18 months (32.0%) and 18 to 24 months (31.8%). The assessment of crossing percentiles was not a part of the present study aims. However, this is a future step for describing the KPH population for local clinicians.

### 4.8 Strengths and Limitations

This sample provides a longitudinal look at early factors related to later child BMI, which is a strength of these data. These data were not collected for research
purposes but rather for the health care of members. Thus data measurement and entry error is expected. Methods were developed for data cleaning, inspecting growth data, and processing data for use in this research study. However there are certain issues that are beyond our control and should be acknowledged. For example, when measuring lengths of infants, they should be lying supine length up through age 24 months. It is possible that if the child was able to stand, clinical staff might measure the child’s standing height, which could affect child measures by 0.4 to 2.3 cm from 18 – 36 months. This is a limitation that is acknowledged; however only weights/lengths up through 24 months were examined, which would decrease the number of children measured using standing height.

Ethnic data are self-reported and gathered from several sources for the EMR to assure completeness of the data. Coming from different sources may introduce bias although most of the data now come from the personal history sheet and are coded by a standard method for the VDW. Another issue is the difficulty in separating mixed ethnic groups, such as the use of Native Hawaiian even if persons are part-Hawaiian combined with any other race.

A strength of this study is the access to actual measures versus reported measures for birth information and for maternal weights and heights. The KPH EMR allows for capture of diagnostic and medical information that is comprehensive and contains standardized language. This allows for control of factors such as GDM unavailable in other data sets. Self-reported data are common among other studies and are associated with subject over- and under-reporting. Underestimated maternal pre-pregnancy weights have been shown to overestimate associations of maternal BMI and birth outcomes. A suggestion is to be able to link pregnancy data with measured pre-conception weights from medical records or to obtain weights. The limitation, however, is the dependency on regular attendance at visits and the need for medical care to be captured in the KPH EMR. For example, maternal information is often not available before women know that they are pregnant, unless they had a recent pregnancy or came in for sick care.

Children with congenital anomalies present at birth or born preterm may influence birth size, infant growth, and later BMI. Use of EMRs provides the ability to look at these factors. Only one other study reviewed was able to exclude children with
conditions that may influence infant growth. That study conducted a subanalysis excluding children (n = 87 of 888, 9.8%) with similar conditions: systemic disease (5.38%), chromosomal or congenital abnormalities (3.84%), or abnormalities of heart (0.11%), gastrointestinal tract (0.46%) or urogenital tract (0%). Preterm births (defined as < 37 weeks gestational age) are also associated with altered growth trajectories. In the United States, preterm births decreased to 12.2% in 2009 from 12.8% in 2006. In this sample no major differences were noted between those with congenital anomalies and preterm births and for those without these conditions.

The present study did not include birth weight as part of the estimation of change in infant growth. This was done in order to examine the effect of birth weight, birth length and birth BMI on infant growth adequately. Most studies have measured change in infant growth by including the birth measure, which introduces error if birth weight is an independent variable and is part of the intermediate variable, in this case, infant growth. However, it could be a limitation that the first large gains during infancy in the first couple of months of growth were not included.

Infant time periods vary in terms of growth with most weight gain occurring in the first year. This study did not examine infant time periods of growth and relation to BMI at age five years. Previous studies have determined weight gain during certain time periods during infancy were associated with later child overweight. Other studies have found no difference between 0 – 6, 6 – 12, 12 - 18 months.

It is difficult to quantify a meaningful value of BMI at age five years and associated later health risk since there is not enough research to inform clinical use of BMI as a diagnostic tool for later disease risk in children. However, we can classify BMI into categories of overweight/obese, which are known risk factors for early maturation, development of insulin resistance, and other child co-morbidities. Use of BMI category as a screening tool for individual risk is “poor”. The link of BMI during childhood with metabolic disturbances, such as insulin resistance, triglycerides in later adulthood, is not clear. However, BMI is a proxy for adiposity which is a determinant of insulin resistance. Therefore it is suggested that we move in the direction of adiposity standards by gathering direct measures of body fat.
A major limitation is the timing of data pulled from the KPH EMR in 2010. This was done to obtain a retrospective sample of children born in 2004 and 2005. The EMR was not complete until 2005 and Obstetrics/Gynecology department electronic entry was done later than this. Information was collected mostly on paper and entered at a later time. This limited the sample numbers, based on availability of data for specific maternal variables. It is possible that women are seeing their PCP before pregnancy; then, once pregnant, they will see an OB/GYN (pre-pregnancy vs 1st pregnancy). Therefore we find fewer first pregnancy weights, due to incompleteness of OB/GYN electronic notes in the years at which data are pulled. However, the first pregnancy weights available were not always in the first trimester; therefore, pre-pregnancy weights were used to calculate BMI. This also made calculation of GWG a challenge since the actual duration of weight gain varied largely between participants who had a first and last weight. For this reason, maternal weight gain provided on child birth certificates was used in a subanalysis.

The information gathered on infant feeding is limited and accessible only via the text as Smart Set phrases in the doctor’s electronic notes. The contribution of exclusive breastfeeding to child BMI cannot be demonstrated in this study and requires further study. This is due to the limits of defining breastfeeding through text information. Further work in the EMR needs to be done to be able to separate out breastfeeding and/or formula feeding, which is also noted to be important to differentiate because formula fed babies grow faster than breast-fed babies.\textsuperscript{166, 245} Also the protein content in formula is higher than in breast milk,\textsuperscript{245} which may have deleterious effects, including increased insulin growth factor 1 secretion, which is associated with faster weight gain and higher adiposity.\textsuperscript{245} Overfeeding is also a known concern for excessive caloric intake via bottle or through added calorie sources such as infant cereal.\textsuperscript{108, 246, 247}

Early introduction of solid foods post-weaning is also associated with later child overweight.\textsuperscript{248-250} Capturing this information in the EMR is a challenge because it also falls within Smart Set text indicated by physicians. This is also complicated by lack of a standardized way of capturing this information. Mothers will feed early based on their perception of infant hunger or large size of infant,\textsuperscript{250, 251} which may be more harmful than helpful in terms of overfeeding. The foundations for flavors and textures are set early, as children transition from a liquid diet in early infancy. Children should experience a
variety of foods and foods should be nutrient-rich. They should also be provided with repeated opportunities to try different foods so infants can learn to like the taste of a new food. 108, 252, 253

Infant sleep patterns and excess television viewing have also been associated with child overweight. 107, 254, 255 This is information that was also unavailable through the EMR. In addition, diet and physical activity patterns during childhood could influence BMI at age four to six years. Unhealthful eating habits may be highly influenced by what is provided in the first two years of life.
CHAPTER 5. CONCLUSION

This retrospective, longitudinal study examined the role of birth size and infant growth with child BMI at age five years. Birth weight adjusted for gestational age was an independent predictor of BMI at age five years but not birth length or functions of relative weight-for-length. Maternal pre-pregnancy weight, birth weight, and change in infant weight and length, predicted child BMI at age five years. The relationship of a higher birth weight and higher child BMI at age five years was not explained by change in infant weight, length, or BMI. It is plausible that birth weight may serve as a mediator for the prenatal and maternal factors and later child BMI period.

Tests for linearity showed no evidence of a U-shape relationship after including squared terms of birth weight in the model. This justifies accepting the linear relationship between birth weight and child BMI at age five years. Absolute pre-pregnancy weight of the mother and the child’s birth weight as opposed to maternal BMI and child birth length were better predictors of child BMI at age five years.

Race/ethnic differences in birth weight and change in infant weight were observed between Other PIs and White and Asian race/ethnic groups. Exploratory plots of BMI trajectories among race/ethnic groups suggest differences after age one year. This may be an indicator of other unmeasured factors (e.g., transition to solid/table foods) that that differ by race/ethnic groups that should be explored.

5.1 Public Health Implications

The significance of this observational study is identification and validation of key markers for early prevention of child overweight before age five years. The health care system can be used to identify and target these key areas for intervention. Application of these results would be beneficial to clinicians for improving their assessment and identification of those at risk for child overweight. The known presence of race/ethnic differences in birth size and growth patterns emphasizes the importance of reconsidering how standards apply to these groups and whether there should be closer examination based on these differences.
The infant time period of birth up to age 24 months is heavily influenced by the immediate family environment which then transitions to the external environment during preschool and school age years. This may be an influential time to modify and instill dietary and lifestyle changes in the family to set the child on the right path for health.

Population-wide benefit of prevention of chronic disease can begin with the exploration of the improvement of the health of women of child-bearing age prior to pregnancy. A healthy lifespan perpetuates future health in children who become healthy men and women. Healthy mothers have healthy babies. Preparing young woman for a healthful lifestyle can result in a ‘trickle-down’ effect of health through her own future, her future children and other family members. Attention to the presence of these key factors may provide targets for early intervention.

5.2 Future Studies

Use of the KPH EMR to assess risk for child overweight with consideration for maternal pre-pregnancy weight, birth size, infant growth, and child overweight is needed. Further assessment of the predictive ability of these factors would be beneficial for clinical application and guidance for KPH physicians in improving prevention of child overweight. In the identification of child overweight, further research on race/ethnic-specific clinical assessment would be helpful. Validation of the use of standard methods for assessment of growth using the new WHO growth charts in the KPH population could provide further information on race/ethnic differences. Marked differences in body size and growth trajectories in Pacific Island children were compared with WHO growth standards of 2006, indicating race/ethnic differences in growth. Examination of differences in adiposity or fat mass gain in race/ethnic groups would be additive to BMI screening and could assist in predicting the onset of early pubertal development. In addition, this expanded screening would prevent future deleterious metabolic risk factors in early adolescence. Exploration of non-invasive anthropometric measures (e.g., skinfolds) to indicate fatness at an early age and reference standards for the KPH population should also be considered.

Patterns of good health start early and are likely to be dependent on previous exposure and experience. A healthful lifestyle during the child-bearing age can be
influential on the next pregnancy period, and later infant/toddler/family health. Early intervention should begin with an understanding of the needs during this time period. Since maternal pre-pregnancy weight was a primary indicator of child BMI at age five years, assessment of the feasibility of a ‘well-woman’ or preconception care early prevention program is needed. Preconception care promotes the health of women of reproductive age with the goal of improving pregnancy related health outcomes.256 The goal is to provide risk screening, health promotion, and interventions as a part of routine health care. A needs assessment would be helpful in understanding current practices at KPH that support preconception care and exploring the feasibility of developing a program further. An example of this would be to include designing an early intervention for changing health behaviors in preparation for pregnancy in overweight women. Furthermore, determining an innovative and effective way to deliver this program should be explored by engaging women to be a part of the planning, which would also assure successful implementation and sustainability. Attitudes and perceptions of health, as well as motivators and barriers to obtain good health, should be assessed. In these modern times, women multi-task and have busy lifestyles, which calls for a different approach to supporting healthy behaviors in order to achieve good health. Assessment of different media or health technology efforts that are tied to the health care system that would facilitate preconception care should be assessed in order to create a sustainable program. Race/ethnic differences in seeking health care and socioeconomic factors should also be explored. Providing guidance and rationale for formation of these early health habits are key during this stage in life and will support the maintenance of these skills and modeling for their children.

Optimal maternal health during pregnancy is conducive to a healthy pregnancy and baby. Future studies should focus on interventions that target maintenance of healthful weight gain based on current IOM guidelines.215 Maternal nutrition is related to maternal obesity. Creation of new methods for teaching or supporting healthful food choices and prescribed activity should be explored. During the transitional periods of infant feeding (from breast to introduction of solid foods, in late infancy and from the toddler to preschool age) introduction to new tastes and environments are additional key areas to target. During this time, children are still largely influenced by their parents and
what their parents eat. Evaluation of the depth of parents’ knowledge upon leaving the health care system of what to feed or how to feed their child should be assessed. For example, repetitive feedings of fruit or vegetables for a period of time is important to increase exposure and acceptance of these foods.\textsuperscript{253} Future studies should also assess the adequacy and availability of learning tools that are essential to mothers and/or fathers in order to begin healthful feedings that are compatible with their culture, family structure (e.g., single parent, siblings), and lifestyle.

Furthermore, consideration for future exploration of infant feeding information gathered by the KPH EMR and areas for improvement could be beneficial to improving health care. A future secondary analysis could involve a deeper understanding of race/ethnic, infant feeding, and maternal information in the improved KPH EMR. The most recent years will have more complete information and can provide a validation of gaps in capturing the information which might be indicative of the need for intervention.

It is imperative that children have healthy beginnings that will foster and enable their development into healthy adults. Early identification of determinants of child overweight is part of primary prevention to deter unfavorable consequences of subsequent obesity. Early intervention can instill perpetuation of healthy habits in mothers who can model and support a healthy start to life for their child and for future generations.


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