Dietary Behaviors of Adults Born Prematurely May Explain Future Risk for Cardiovascular Disease

Mastaneh Sharafi a, Valerie B Duffy a*, Robin J Miller b, Suzy B Winchester c, d, Tania B. Huedo-Medina a, Mary C Sullivan d.

Affiliations: a Department of Allied Health Sciences, University of Connecticut, Storrs, CT; b School of Nursing, University of Connecticut, Storrs, CT; c Brown Center for Study of Children at Risk Women & Infants Hospital, Providence, RI; d College of Nursing, University of Rhode Island, Kingston, RI

* Address correspondence to: Valerie B Duffy
University of Connecticut
Department of Allied Health Sciences
College of Agriculture and Natural Resources
358 Mansfield Road, Unit 2101
Storrs, CT 06269-2101
Phone: (860) 486-1997
Fax: (860) 486-5375
E-Mail: valerie.duffy@uconn.edu

Abbreviations: ANCOVA – Analysis of Covariance; BMI – Body Mass Index; CVD – Cardiovascular Disease; FT-adults – Full term born adults; HDL – High Density Lipoprotein; HEPI – Healthy Eating Preference Index; HPTs – Healthy Preterm Infants; LDL – Low Density Lipoprotein; MPTs – Medical Preterm Infants; NPTs – Neurological Preterm Infants; PT-adults – Preterm born adults; SGA – Small for Gestational Age Preterms; TC – Total Cholesterol.
Abstract

Being born prematurely associates with greater cardiovascular disease (CVD) risk in adulthood. Less understood are the unique and joint associations of dietary patterns and behaviors to this elevated risk among adults who are born prematurely. We aimed to model the associations between term status, dietary and lifestyle behaviors with CVD risk factors while accounting for the longitudinal effects of family protection, and medical or environmental risks. In wave-VIII of a longitudinal study, 23-year olds born prematurely (PT-adults, n=129) and full term (FT-adults, n=38) survey-reported liking for foods/beverages and activities, constructed into indexes of dietary quality and sensation-seeking, dietary restraint and physical activity. Measured CVD risk factors included fasting serum lipids and glucose, blood pressure and adiposity. In bivariate relationships, PT-adults reported lower dietary quality (including less affinity for protein-rich foods and higher affinity for sweets), less liking for sensation-seeking foods/activities, and less restrained eating did FT-adults. In comparison to nationally-representative values and the FT-adults, PT-adults showed greater level of CVD factors for blood pressure and serum lipids. In structural equation modeling, dietary quality completely mediated the association between term status and HDL-cholesterol (higher quality, lower HDL-cholesterol) yet joined term status to explain variability in systolic blood pressure (PT-adults with lowest dietary quality had highest blood pressures). Through lower dietary quality, being born prematurely was indirectly linked to higher cholesterol/HDL, higher LDL/HDL and elevated waist/hip ratios. The relationship between dietary quality and CVD risk was strongest for PT-adults who had developed greater cumulative medical risk. Protective environments failed to attenuate relationships between dietary quality and elevated CVD risk among PT-adults. In summary, less healthy dietary behaviors contribute to elevated CVD risk among young adults who are born prematurely.

Key words: preterm; dietary quality; structural equation modeling; food preference; restraint, food neophobia; cardiovascular disease
1. Introduction

Adults who were born prematurely can have increased rates of risk factors for cardiovascular disease (CVD) (Rogers & Velten, 2011; Sipola-Leppanen et al., 2014), including elevated blood pressure (de Jong, Monuteaux, van Elburg, Gillman, & Belfort, 2012; Parkinson, Hyde, Gale, Santhakumaran, & Modi, 2013), impaired lipid metabolism (Parkinson et al., 2013), insulin resistance (Finken et al., 2006; Hofman et al., 2004) and greater central adiposity (Barbieri et al., 2009). These risk factors may result from the prematurity, including adverse prenatal environments with maternal health complications (fetal programming), and/or challenges in developing healthy diets, including food sensitivities and intolerances (Barbieri et al., 2009; Behrman & Butler, 2007; Kaseva et al., 2013; Silveira et al., 2012), food neophobia (Migraine et al., 2013) and fussy eating (Samara, Johnson, Lamberts, Marlow, & Wolke, 2010), which parallels avoidance of risk taking (Hack et al., 2012; Roberts et al., 2013) and sensation seeking (Alley & Potter, 2011; Allin et al., 2006; Pliner & Melo, 1997). Intrauterine growth restriction with or without prematurity is linked to greater preference for sweets (Ayres et al., 2012; Barbieri et al., 2009; Silveira et al., 2012), salty taste (Stein, Cowart, & Beauchamp, 2006) and lower affinity/intakes of protein-rich foods and fruits (Kaseva et al., 2013; Migraine et al., 2013) in children and higher intakes of carbohydrates (Barbieri et al., 2009) and lower intakes of fruits, vegetables (Kaseva et al., 2013) and alcohol (Cooke, 2004; Roberts et al., 2013) in adults. A recent analysis of a large prospective cohort study suggested the additive effects of unhealthy lifestyle (scored from diet, physical activity, smoking, alcohol consumption and BMI) and low birth weight on greater relative risk of type 2 diabetes through multivariate logistic modeling (Li et al., 2015), yet the study sample had
lower representation of low-birth weight, relied on self-reported birth weight and did not control for the effect of being born prematurely. Appropriate self-regulation or restraint could counteract the negative effects of less healthy dietary behaviors (Johnson, Pratt, & Wardle, 2012; Tomiyama, Moskovich, Haltom, Ju, & Mann, 2009; Wardle & Beales, 1987).

Linking diet with risk of chronic disease in a longitudinal study requires assessment instruments that capture habitual dietary behaviors and are low burden to the participants. Multiple dietary records and/or food frequency surveys may or may not reflect habitual dietary intake, are time and labor intensive, and challenged by misreporting (Thompson & Subar, 2013). The present study used reported liking/disliking of foods and beverages as a rapid proxy of dietary intake that may capture more habitual behaviors. Survey reporting of food liking links genetic variation in oral sensation with dietary intake as adults (Duffy, Hayes, Sullivan & Faghri, 2009; Törnwall et al, 2014), assuming that genetic variation influences development of food preferences (Mennella, Pepino, & Reed, 2005; Pallister et al., 2015) and that, overtime, we eat what is liked and avoid what is not. Survey liking correlates with reported intake (Erinosho et al., 2015; Tuorila et al., 2008), nutritional biomarkers, including carotenoid (Scarmo et al., 2012) and fatty acid (Hutchins-Wiese, Duffy, Watkins, Li, & Kenny, 2013) status, variety of metabolites (Pallister et al., 2015) and adiposity (Duffy, Hayes, Sullivan, & Faghri, 2009; Duffy et al., 2007; Peracchio, Henebery, Sharafi, Hayes, & Duffy, 2012). Inclusion of non-food items on a liking survey supports the ability to compare food liking across individuals by generalizing the scale (Bartoshuk et al, 2006) and can capture affinity for sensation seeking foods and activities (Terasaki & Imada, 1988). Responses from a liking
survey can be formed into a dietary quality index that has acceptable internal consistency
as well as construct and criterion-related validity with the ability to predict adiposity and
nutritional biomarker, carotenoid status (Sharafi, Peracchio, et al., 2015).

The present study aimed to extend previous research by assessing the direct and
indirect relationships between dietary behaviors and measures of CVD risk in adults who
were born prematurely (PT-adults) versus full-term (FT-adults) via Structural Equation
Modeling (SEM). SEM is a relatively novel multivariate technique that is proposed to
overcome limitations of the traditional statistical methodologies by allowing testing direct
and indirect (e.g. mediation) relationships among multiple variables (A. F. Hayes, 2009).

CVD is a complex, multifactorial disease process and although SEM seems very
promising in the study of complex pathways, it has been rarely been used in the field of
diet related CVD risks (Antonogeorgos et al., 2012). Specifically, we hypothesized that
PT-adults would report greater preference for high fat/sweet/salty foods, lower preference
for healthy foods, and less dietary restraint on eating. Consistent with risk avoidance
(Allin et al., 2006; Hack et al., 2012), we hypothesized that PT-adults would report
lowest affinity for sensation-seeking activities and foods. Finally, since environment
influences early development (Bradley et al., 1994; M. M. McGrath & Sullivan, 2003;
Pridham, Brown, Sondel, Clark, & Green, 2001), we examined how measures of risk and
protective environments during childhood influenced relationships between dietary
quality and CVD risk factors in adults who were born prematurely.

2. Material and Methods

2.1. Design and Subjects
This study was part of a wave VIII of a prospective longitudinal study of premature infants. The 215 premature and full-term infants were recruited at birth with follow-up assessments at ages 18m, 30m, 4y, 8y, 12y, 17y and now at age 23. The recruitment at birth occurred between 1985-1989 from a Level-III neonatal intensive care unit in a specialty hospital in southern New England. Parents were recruited by research nurses and provided written consent. The recruitment criteria, identified \textit{a priori}, included neonatal diagnoses, birth weight, absence of maternal mental illness, and English as a primary language. Five groups were classified by neonatal morbidity. Full-term infants \((n = 55)\) were born from mothers with uncomplicated labor and delivery, absent of neonatal diagnoses, \(\geq 2,500\) grams birth weight, \(\geq 38\) weeks gestational age, and were recruited from the same medical center at the same time as the preterm infants. All preterm infants were \(<37\) weeks gestational age, birth weight \(<1850\) grams, and classified into four groups based on their neonatal illness. Healthy preterm infants (HPTs; \(n = 33\)) had no medical or neurological illness. Preterm infants with medical illness (MPTs; \(n = 60\)) had bronchopulmonary dysplasia (defined as oxygen requirement at 28 days of life), respiratory distress syndrome, necrotizing enterocolitis (Bell, 1978), and/or sepsis. Preterm infants with neurological illness (NPTs; \(n = 36\)) had Grade III & IV IVH (Papile, Burstein, Burstein, & Koffler, 1978), meningitis, and/or shunted hydrocephalus. Small for Gestational Age (SGA; \(n = 31\)) preterm infants had birth weights below the 10th percentile for length with/without neonatal illness (Lubchenco, Hansman, & Boyd, 1966). Socioeconomic status (SES) was equally distributed within and across neonatal groups at recruitment. Fewer than 10% of the parent(s) declined participation in the study.
In wave VIII, participants were contacted within 6 months of their 23rd birthday. The sample at age 23 years consisted of 180 of the original 215 participants recruited at birth (84% retention rate from birth). Reasons for attrition ($n = 35$) included travel/scheduling issues, military deployment, or inability to locate/contact. Those who dropped from the study between the birth time point and age 23 did not favor a specific neonatal group and there were no differences between those who participated and those who dropped out at age 23 in neonatal illness, SES, parent education, marital status, or race.

Of the 180 subjects, 13 did not complete the dietary surveys, leaving a final sample of 167 (129 PT-adults and 38 FT-adults) described in Table 1. Informed consent was obtained during the home visit, followed by collection of fasting capillary blood by the research nurse. The laboratory visit included a physical assessment, health interviews and dietary questionnaires. Informed consent was obtained from parents at recruitment, and at each time point (with the exception of age 23 years). Child assent was obtained at ages 8 years, 12 years, and 17 years, and informed consent by study participants at age 23 years. The reported health information was verified by medical record. Trained research staff collected all data, with 90%+ inter-rater reliability (Sullivan, 2008) and were blinded to term group. The university and hospital Institutional Review Boards approved the study at each time point. Study participants received $100 for participating at age 23 years.
Table 1. Descriptive characteristics of sample (N=167) at age 23 years.

<table>
<thead>
<tr>
<th></th>
<th>All (n=167)</th>
<th>Term status</th>
<th>Preterm subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Full-term (n=38)</td>
<td>Preterm All (n=129)</td>
<td>HPTs (n=24)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88</td>
<td>20</td>
<td>68</td>
</tr>
<tr>
<td>Male</td>
<td>79</td>
<td>18</td>
<td>61</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>144</td>
<td>33</td>
<td>111</td>
</tr>
<tr>
<td>African-American</td>
<td>15</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>SESa, b</td>
<td>40±13.8</td>
<td>41.1±14.0</td>
<td>39.7±13.8</td>
</tr>
<tr>
<td>Physical activityc</td>
<td>7.6±2.9</td>
<td>7.4±3.0</td>
<td>7.6±2.9</td>
</tr>
<tr>
<td>Moderate (days/week)</td>
<td>1.6±0.7</td>
<td>1.6±0.1</td>
<td>1.7±0.1</td>
</tr>
<tr>
<td>Vigorous (days/week)</td>
<td>1.4±0.6</td>
<td>1.4±0.7</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Smoke^d</td>
<td></td>
<td></td>
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<tr>
<td>Never (0 times/day)</td>
<td>9</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Moderate (1-3 cigarettes/day)</td>
<td>6</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Frequent (≥4 cigarettes/day)</td>
<td>7</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>1755±96</td>
<td>3433±40</td>
<td>264±323</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>32.3±4.7</td>
<td>39.9±0.7</td>
<td>30.0±2.5</td>
</tr>
<tr>
<td>Adult BMI^e</td>
<td>26.0±5.8</td>
<td>26.6±6.4</td>
<td>25.8±5.7</td>
</tr>
<tr>
<td>Underweight (&lt;18.5)</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Normal (18.5&lt;25)</td>
<td>73</td>
<td>14</td>
<td>59</td>
</tr>
<tr>
<td>Overweight (25&lt;30)</td>
<td>56</td>
<td>10</td>
<td>46</td>
</tr>
<tr>
<td>Obesity (≥30)</td>
<td>33</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

HPTs=Healthy Preterm infants; MPTs=Medical Preterm infants; NPTs=Neurological Preterm infants; SGA=Small for Gestational Age infants.
a Mean±SD.

b SES (socioeconomical status defined by Hollingshead Four-Factor Index at age 23).
c Physical activity score is sum of weighted moderate and vigorous physical activities.
d Missing data is due to participants opting not to answer to the question. There were no differences between those who completed smoking questions versus those who did not on demographic and health-related variables.
e BMI (body mass index) is weight (kg)/height squared (m²).

f Significant mean difference from full-term (P < .001).
g Among preterm subgroups, significant difference from full-term (MPTs (P < .05), NPTs (P < .01), and SGA (P = .001).
h Among preterm subgroups, significant difference from HPTs and SGA (Ps <0.001).
i Significant variance difference from NPTs and MPTs (Ps < .05).

2.2. Measures

Table 2 shows when the dietary and lifestyle (smoking, physical activity) behaviors, risk and protective indices as well as CVD risk factors were collected across the longitudinal study.

<table>
<thead>
<tr>
<th>Table 2. Timing of data collection across the prospective study of premature infants</th>
<th>Birth</th>
<th>18 months</th>
<th>30 months</th>
<th>Age 4</th>
<th>Age 8</th>
<th>Age 12</th>
<th>Age 17</th>
<th>Age 23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Medical Risk</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Cumulative Protection Index</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Environmental Risk</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Dietary intake (liking survey)</td>
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<td></td>
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<tr>
<td>Dietary restraint</td>
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<tr>
<td>Food neophobia</td>
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<tr>
<td>Lifestyle behaviors</td>
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<tr>
<td>CVD risk factors</td>
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</tbody>
</table>

2.3 Diet and Healthy Eating Preference Index

Using a general Visual Analog Scale (Byrnes & Hayes, 2013), participants reported liking/disliking for 47 foods/beverages and 19 non-food items. Liking scores were treated continuously (±100 points) for conceptual categorizing into statistically-reliable
preference groups with latent variable analysis (Figure 1). A “variety” score was formed from the number of liked (scale score ≥ 35) nutrient-dense items (e.g., fruits, vegetables, whole grains) and mathematically converted to ±100 score. Consistent with diets for CVD prevention (Eckel et al., 2013) and other dietary indices [e.g., Healthy Eating Index, Diet Quality Index (Kourlaba & Panagiotakos, 2009)], conceptual weights were assigned prior to averaging into a dietary quality index, Healthy Eating Preference Index (HEPI): fruits/vegetables (+3), protein (+1), fat (-3), sweets (-3), salty food (-3), wine (+2), and variety score (+2). Specific to red wine, moderate consumption is part of Mediterranean diet that associates with favorable effects on cardiovascular risk factors (Rees, et al., 2013), possibly through improved glucose metabolism (Chiva-Blanch et al., 2013) and lipopolysaccharide concentrations (Clemente-Postigo et al., 2013). The averaging liking for wine in the current study suggested that most participants were moderate drinkers. From previous work in our laboratory, the HEPI among preschoolers showed good construct and criterion related validity and adequate reliability, comparable to healthy eating indexes formed from food frequency or dietary records (Sharafi, Peracchio, et al., 2015) and was a significant predictor of carotenoid status and adiposity.

2.4. Other Dietary and Lifestyle Behaviors

The Revised Restraint Scale (10-item self-report questionnaire) was used to identify dietary restraint from two subscales: concern for dieting, weight fluctuation (Herman & Polivy, 1980). A Revised Food Neophobia Survey (Ritchey, Frank, Hursti, & Tuorila, 2003) assessed the avoidance of new and/or spicy foods (Alley & Potter, 2011; Alley, Willet, & Muth, 2006)—two items formed a single question about liking multi-cultural foods with responses on 5-point frequency versus original Likert scale (Bartoshuk, Duffy,
Hayes, Moskowitz, & Snyder, 2006). The neophobia score was the average frequency of neophobia (3 of 7) minus of neophilia (4 of 7) items (Ritchey et al., 2003). The dietary restraint and food neophobia scores were statistically reliable ($\alpha > 0.7$).

A sensation seeking latent variable was formed from liking (Duffy et al., 2009; Duffy et al., 2007) for spicy foods (Byrnes & Hayes, 2013) (spicy rib, jalapeno, spicy chips; $\alpha = 0.76$) and risk-taking behaviors (driving fast, smoking cigarettes, drinking vodka/gin, walking barefoot; $\alpha = 0.60$) and food neophobia score (reverse coded).

The Personal and Social Development Questionnaire (Jessor, Costa, & Turbin, 2003) was used to assess smoking and physical activity. The subjects also responded to the number of cigarettes per day within the past 6 months. Responses ranged from never (0/day), moderate smoker (1-3 cigarettes/day), and frequent smoker (4 cigarettes/day to 2 packs or more). The associations between reported liking and frequency of smoking was tested to assess whether reported liking could be used as a proxy for smoking.

Participants responded to the number of hours per week of moderate physical activity (e.g., brisk walking, you still sweat, but may carry on a conversation), vigorous physical activity (e.g., running, you still sweat, have a rapid heart rate, and can only talk in short phrases) within a typical week within the past 6 months. Moderate and vigorous physical activity ranged from minimal (0-2 hours/week, coded as 1), moderate (3-5 hours/week, coded as 2) and intense (6 or more hours/week, coded as 3). A physical activity score was formed from the sum of weighted codes of moderate (weight = +2) and vigorous (weight = +3) physical activity (Sharafi, Faghri, Huedo-Medina, Minski, & Duffy, 2015).

2.5. Risk and Protective Indexes
A cumulative medical risk index was comprised of neonatal variables, and medical and neurological factors at birth, toddler, preschool, school-age, and adolescence, obtained from medical records and physical health assessments administered by research nurse at each time point, and developed using confirmatory factor analysis with appropriate fit statistics (Winchester, Sullivan, & Msall, 2014). The neonatal factors were the Hobel neonatal illness (Hobel, Hyvarinen, Okada, & Oh, 1973), length of hospital stay, birth weight, gestational age. Medical neonatal factors were medical health status, necrotizing enterocolitis, bronchopulmonary dysplasia, and hours of oxygen. Neurological neonatal factors were neurological health status, intraventricular hemorrhage, and shunted hydrocephalus. Medical health status was classified as normal (no abnormalities), suspect (continued chronic respiratory, cardiac murmurs, referral for hearing, orthopedic), and abnormal (asthma, allergies, diabetes, and/or autoimmune deficiencies). Neurological health status was classified as normal (no abnormalities), suspect (fine motor weakness, unilateral sensorineural hearing loss, uncorrected vision problems, atypical neurologic findings in tone, reflexes, gait or movement with no specific diagnosis), and abnormal (cerebral palsy, blindness, deafness, shunted hydrocephalus, uncontrolled seizures, and attention-deficit/hyperactivity disorder (Niswander & Gordon, 1972; Prechtel & Beitema, 1967).

Environmental risk was assessed at birth using the Hollingshead Four-Factor Index (Hollingshead, 1975), an indicator of social status and comprised of maternal and paternal education and occupation levels.

A cumulative protection index was formed from variables in the environment proximal to the child at birth, 4 years, 8 years, and age 12 years (Winchester et al., 2014).
Included in the index was stimulation within the home environment [Home Observation for Measurement of the Environment; (Caldwell & Bradley, 2001)], maternal perception of child vulnerability (M. M. McGrath, 1989b), and maternal self-esteem (M. M. McGrath, 1989a), and maternal involvement as well as maternal control style measured at 4, 8 and 12 years from laboratory paradigms. The cumulative protect index was developed using confirmatory factor analysis with appropriate fit statistics (Winchester et al., 2014).

Since breastfeeding data only were available for 59% of PT-adults and 74% of FT-adults (61 of 99 PT-adults were breastfed versus 21 of 28 FT-adults), sub-analyses were not conducted. Mothers reported to either breastfeed exclusively for 5.6 months (M=5.6 months, SD=6.2, Median=4.0, 0-28 months) or a combination of formula and breastmilk for 5.4 months (M=5.4, SD=8.3, Median=3.0, range=0-48 months).

2.6. Cardiovascular risk factor assessment
Blood pressure, adiposity, serum lipids and blood glucose served as CVD risk factors. For blood pressure, participants rested in a sitting position for approximately 5 minutes where a registered nurse determined their cuff size (where bladder width is 40% of the arm circumference) and bladder length (80% of the circumference of the arm). Blood pressure was recorded for three times in 5-minute intervals using a calibrated automated (Dinamap) sphygmomanometer. The average of three systolic blood pressure (SBP) measurements was analyzed.

Adiposity was measured by waist/hip ratio and body mass index. Using a 72” paper tape measure, waist was the circumference at the umbilicus and hip at the widest area of the hips. Participants were instructed to take a breath, exhale, and then take the
waist measurement to avoid a falsely lower reading. Height was measured while standing against a wall-mounted stadiometer and weight with a medical scale (calibrated before each weighing), both without shoes, for BMI calculation. For capillary blood analysis, participants were asked to fast for 8-10 hours before the assessment using the CardioChek/PA meter (Polymer Technology Systems, Inc, Indianapolis, IN) (Panz, Raal, Paiker, Immelman, & Miles, 2005) for serum glucose, total cholesterol (TC), High Density Lipoprotein (HDL), and triglycerides. Low Density Lipoprotein (LDL) was derived from the Friedewald formula: LDL = TC - HDL - (TG / 5) (Friedewald, Levy, & Fredrickson, 1972). Total cholesterol/HDL (TC/HDL) and LDL/HDL ratios also were analyzed as CVD risk factors.

2.7. Statistical analysis

Data were analyzed using SPSS (version 17.0; SPSS Inc, Chicago) and M plus (version 7.0; Mplus Inc, Los Angeles) software. Significance criterion was \( P \leq .05 \). Descriptive statistics characterized participants by term status and preterm subgroups, comparing the values to published norms where appropriate using the standardized mean difference \( (d) \) the effect size index (Hedges, 1981). Latent variable analysis formed HEPI and sensation seeking. For the analysis, preterm subgroups were combined in one group of PT-adults as preliminary analysis showed no significant differences in their diet and CVD risk factors. The power analysis with medium effect size \( (d = 0.5) \) determined that 110 PT-adults and 32 FT-adults were adequate to capture mean differences between adults born preterm versus full term \( (\alpha = 0.05, 1-\beta = 0.80) \).
Analysis of covariance (ANCOVA) initially assessed for differences between PT-adults and FT-adults regarding dietary, risk taking, and index variables. Multiple regression analysis was conducted to describe the relationship among the dietary and sensation seeking variables as well between birth weight and these variables in PT-adults. Based on the results of the ANCOVA and regression analysis, a model was developed and tested with SEM in order to identify the direct and indirect influences of term status on CVD risk factors with potential effects of dietary (HEPI, dietary restraint, sensation seeking latent variable), other lifestyle factors (physical activity, liking for smoking as individual variable), demographic (gender, SES) variables, and adiposity. To detect a medium effect size for a SEM including criteria for adequate model fit were non-significant chi-square [$\chi^2 (p > .05)$] or $\chi^2$ to df ratio ($\chi^2$/df) < 2, with Comparative Fit Index (CFI) $\geq 0.92$ and Root Mean Square Error of Approximation (RMSEA) $\leq 0.05$ (Ullman, 2001). The power analysis with a medium effect size ($d = 0.5$) for the main path and small effects for each other paths and the mediation effects ($d = 0.10$), showed that 100 subjects were required to achieve 98% power with a minimum $R^2 = 0.23$ and a RMSEA < 0.05.

3. Results

As shown in Table 1, FT-adults and PT-adults (or subgroups) did not differ by SES, smoking, exercise level or average BMI. However, HPTs had significantly greater variances in BMI than NPTs and MPTs (Table 1), yet no significant differences in the distributions of overweight and obese individuals. All groups were gender matched.
except for significantly fewer males in SGAs than FT-adults ($\chi^2 = 4.87, P < .05$). As expected, FT-adults had higher birth weights than PT-adults (Table 1).

3.1. Descriptive findings—dietary quality index and subcomponents

In the entire sample, conceptual food groups were formed that varied from most to least liked as follows: sweets, salty, fats, protein, fruits/vegetables, and wine. The highest variability in liking ratings were seen in vegetables, fats, and wine (interquartile ranges $> 45$ in 200 points scale), which indicates that the central 50% of ratings were fairly wide apart. Only 15% of the sample reported liking more than half of the healthier foods/beverages.

The conceptual food groups were then tested by latent variable analysis for internal consistency and overall structure. Figure 1 shows the final items included for each food group and measures of model fit indicating an adequate overall structure for the HEPI. Wine and variety scores added after the latent variable analysis to form the final HEPI score. HEPI score was normally distributed (Shapiro-Wilk = 0.99, $P = 0.26$), averaging $-39.6 \pm 38.0$ SD.
Figure 1. Latent variable model of food groups used to develop Healthy Eating Preference Index (HEPI). Model fit: $\chi^2/df = 1.4$, CFI = 0.94 and RMSEA = 0.05.

PT-adults reported significantly lower dietary quality (HEPI scores) than did the FT-adults ($F = 7.8$, $P < .01$), driven by less liking for wine and protein-rich foods (Table 3). Although non-significant mean differences, PT-adults were distributed to greater liking for sweets—approximately two-third of PT-adults were distributed toward high sweet liking category (> strongly like) while FT-adults more evenly divided across high and low liking categories ($\chi^2 = 4.0$, $P < .05$). The sub-analysis of PT-adults showed that lower birth weight was associated with a greater sweet liking ($b = -0.21$, $P < .05$) and lower HEPI scores ($b = 0.18$, $P < .05$) with no significant associations for fats, protein and salty foods.
Table 3. Healthy Eating Preference Index score and sub-components by term status\textsuperscript{a,b}. 

<table>
<thead>
<tr>
<th>Healthy Eating Preference Index Indicators</th>
<th>FT-adults</th>
<th>PT-adults</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>-24.8 (6.1)</td>
<td>-44.1 (3.3)</td>
<td>.02</td>
</tr>
<tr>
<td>Fruits/Vegetables</td>
<td>21.1 (5.2)</td>
<td>18.1 (2.8)</td>
<td>.72</td>
</tr>
<tr>
<td>Fat</td>
<td>29.9 (6.1)</td>
<td>32.4 (3.3)</td>
<td>.77</td>
</tr>
<tr>
<td>Salty</td>
<td>36.8 (5.3)</td>
<td>42.6 (2.9)</td>
<td>.45</td>
</tr>
<tr>
<td>Protein</td>
<td>30.1 (5.2)</td>
<td>17.9 (2.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Sweets</td>
<td>45.1 (4.5)</td>
<td>51.0 (2.4)</td>
<td>.25</td>
</tr>
<tr>
<td>Wine</td>
<td>31.4 (9.3)</td>
<td>5.2 (5.0)</td>
<td>.02</td>
</tr>
<tr>
<td>Variety</td>
<td>1.0 (6.1)</td>
<td>-7.6 (3.3)</td>
<td>.12</td>
</tr>
</tbody>
</table>

\textsuperscript{a} FT-adults = Full term born adults; PT-adults = Preterm born adults.

\textsuperscript{b} ANCOVA, controlling for influences of gender, BMI and dietary restraint

3.2. Descriptive findings—other dietary and lifestyle behaviors

Across all participants, 13% of males and 35% of females had high dietary restraint [scores > 15 (Allison & Baskin, 2009)]. Controlling for gender and BMI, PT-adults reported lower dietary restraint, including lower weight fluctuation and less concern for dieting, than did FT-adults (Table 4). Dietary restraint scores for PT-adults averaged lower than published norms (Allison, Kalinsky, & Gorman, 1992; Boerner, Spillane, Anderson, & Smith, 2004) (Table 4), while FT-adults did not. In sub-analysis of PT-adults, higher dietary restraint was associated with higher fruits/vegetables liking (b = 0.18, \( P = .05 \)), lower fat liking (b = -0.31, \( P < .001 \)) and higher dietary quality (b = 0.24, \( P < .01 \)). PT-adults’ birth weight was not significantly associated with their dietary restraint.
Table 4. Total restraint and sub-scores were significantly lower among preterm born adults (PT-adults) than full term adults (FT-adults)\(^a\) and lower than norms\(^{b,c}\).

<table>
<thead>
<tr>
<th></th>
<th>FT-adults</th>
<th>PT-adults</th>
<th>F, P values</th>
<th>FT-adults Vs. Norm</th>
<th>PT-adults Vs. Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dietary restraint</td>
<td>-26.8±6</td>
<td>-43.4±3</td>
<td>5.1, .03</td>
<td>-0.27 (-0.37, 0.29)</td>
<td>-2.38 (-0.55, -0.18)</td>
</tr>
<tr>
<td>Weight fluctuation</td>
<td>20.4±5</td>
<td>18.2±3</td>
<td>5.2, .02</td>
<td>0.10 (-0.29, 0.36)</td>
<td>-1.00 (-0.50, -0.13)</td>
</tr>
<tr>
<td>Concern for dieting</td>
<td>33.2±6</td>
<td>31.4±3</td>
<td>3.9, .05</td>
<td>0.67 (-0.17, 0.48)</td>
<td>-0.69 (-0.35, 0.02)</td>
</tr>
</tbody>
</table>

\(^a\) ANCOVA controlling for gender and BMI.  
\(^b\) Norm were pooled data of college-age students (Allison et al., 1992; Boerner et al., 2004).  
\(^c\) Based on calculated effect size (Hedges, 1981).  
\(^d\) Effect size (i.e. standardized mean difference) was the mean of each group individually minus the mean of the norm group, divided by their correspondent pooled standard deviation.

PT-adults were lower sensation seekers than FT-adults (b = -0.26, P = .01) in analysis with the latent variable model of sensation seeking formed from liking for spicy food, liking for thrill seeking behavior and reverse-coded neophobia score (\(\chi^2 = 0.18, df = 2, P = 0.91; CFI = 1.0 \text{ and RMSEA} = 0.0\)). Looking at the food neophobia subscale, across all participants, higher neophobia tended to associate with lower dietary quality, but significantly in sub-analysis of PT-adults (HEPI; b = -0.28, P < .01), including lower liking for Fruits/Vegetables (b = -0.26, P < .01), proteins (b = -0.25, P < .01), and wine (b = -0.28, P < .01) and liking fewer healthy foods (variety score; b = -0.23, P = .01).

For other lifestyle behaviors, the liking and frequency of smoking did not differ significantly between PT- and FT-adults. The liking for smoking cigarettes was associated with frequency of smoking, such that frequent smokers > moderate smokers > non-smokers (F = 5.1, p < .01), suggesting liking for smoking as a proxy for frequency of smoking cigarettes. PT- and FT- adults also reported no significant differences in moderate, vigorous or overall physical activity. The sub-analysis of PT-
adults showed no associations between birth weight and physical activity.

3.3. Relationships among risk and protective indexes, dietary quality and CVD risk factors

As expected, PT-adults had higher cumulative medical risk scores than FT-adults (F = 91.6, P < .001). The cumulative protection index and the environmental risk index and their subcomponents did not differ by term status. These indexes were categorized into high and low groups to test main and interactive effects with term status to predict dietary quality and CVD risk factors. For dietary quality, there was a significant interaction between term status and cumulative protective index—high protection did not improve dietary quality for PT-adults but improved dietary quality 4-fold for FT-adults (Figure 2).
Figure 2. Cumulative family protection index interacts with term status to predict dietary quality scores ($F = 4.42, P < .05$) in ANCOVA controlling for gender, dietary restraint and BMI. PT-adults: Adults born premature; FT-adults: Adults born full-term.

There were no significant main or interactive effects of risk and protective categories on associations between term status and CVD risk factors. There was significant interaction between dietary quality and medical risk ($F = 6.1, P < .05$) on blood pressure; high cumulative medical risk group with low dietary quality had six mm/Hg higher systolic pressure (Figure 3). Similar interaction effects trended for TG, LDL and Waist/Hip ratio ($P \leq 0.2$).
Figure 3. Dietary quality interacts with medical risk status to predict systolic blood pressure ($F = 6.1, P < .05$) in ANCOVA controlling for gender, BMI and term status in all adults ($N = 167$). High medical risk group only consisted adults born prematurely.

3.4. **Structural Equation Models depicting the influences of dietary quality on the term status-CVD risk relationship**

PT-adults, particularly males, had higher systolic/diastolic blood pressures, lower HDL, higher TC/HDL, and LDL/HDL than the reference 2011-2012 NHANES data (Centers for Disease Control and Prevention (CDC) & National Center for Health Statistics (NCHS)) matched for sex and age (large effect size $ds$ of $> 0.8$). In contrast, FT-adults from the current study had similar CVD risk factors. The exception was FT-adults males and females had higher systolic/diastolic blood pressure than NHANES (large effect size $ds$ of $> 0.8$).

Structural equation modeling tested the direct effects of term status on CVD risk factors, controlling for gender (females have favorable risk factors than males), BMI (elevated adiposity was associated with less favorable risk factors) and physical activity.
Among CVD risk factors, SBP and HDL were significantly predicted by term status; PT-
adults had greater SBP \( (b = 0.17, P < .01) \) and lower HDL levels \( (b = 0.14, P < .05) \) than
FT-adults. However, expanding the models showed that dietary quality (HEPI) was a
complete mediator of the term status-HDL relationship (indirect effect = -0.04, \( P < .05 \));
being preterm was associated with lower dietary quality, and lower dietary quality, in
turn, was associated with lower HDL, leaving the association between term status and
HDL non-significant (Figure 4). For the term status-SBP relationship, dietary quality had
no significant complete or partial mediating effect. However, dietary quality \( (b = -0.16, P
< .05) \) and term status \( (b = 0.14, P < .05) \) both significantly predicted SBP with no
significant interaction effect.

\[ \chi^2 = 11.7, \text{df} = 11; P = 0.38; \text{CFI}=0.99 \]

\[ \text{RMSEA}=0.02 \]

Figure 4. Structural equation model showed dietary quality (HEPI) mediating the effect
of term status on HDL-cholesterol level, controlling for the effects of dietary restraint
(restraint), adiposity (BMI), physical activity and demographics (indirect effect
coefficient=-0.04, \( p<.05 \)). Term: full-term = 1, preterm = 2; SES = socio-economic
status; HDL = High Density Lipoprotein; Gender: males = 1, females = 2; arrows are
represented by standardized Beta; The coefficient in parenthesis represents the effect of
term status on HDL-cholesterol before dietary quality was added to the model; * \( P \leq .05 \), ** \( P \leq .01 \), *** \( P \leq .001 \).
In the SEM models with LDL/HDL and TC/HDL, being born premature was associated with lower dietary quality (b = -0.19, \( P = .01 \)), and lower dietary quality, in turn, associated with higher LDL/HDL (b = -0.17, \( P = .01 \)) and TC/HDL (b = -0.16, \( P < .05 \)) ratios. No significant effects were found for fasting glucose or triglycerides. In all of the SEM models, greater dietary restraint was a significant predictor of higher dietary quality (b = 0.15, \( P < .05 \)). Although level of physical activity was not associated with the CVD risk factors, the sub-analysis of PT-adults showed that greater levels of physical activity was associated with lower BMI (b = -0.18, \( P < .05 \)), which in turn, was associated with lower CVD risks. Neither the sensation seeking latent variable nor liking for smoking cigarettes as an individual variable improved the SEM model fit to explain CVD risk factors and thus, was not included in final SEM models.

PT-adults were not different from FT-adults for BMI (Figure 4). However, in separate SEM model, replacing BMI with waist/hip ratio, born prematurely (b = 0.19, \( P < .01 \)) was associated with higher waist/hip ratios. This association weakened to a trend (b = 0.13, \( P = 0.08 \)) when HEPI was added to the model, with HEPI significantly predicting waist/hip ratio (b = -0.14, \( P < .05 \)). The mediation effect of HEPI on term-waist/hip ratio was not significant.

4. Discussion

This study assessed direct and indirect effects of dietary quality and dietary behaviors on cardiovascular disease risk factors in a prospectively followed sample of young adults born prematurely versus a full-term comparison group recruited at the same time. Adults born prematurely reported less healthy dietary behaviors as well as lower
sensation seeking behaviors than the full-term peers. For measured CVD risk factors, preterm adults exceeded the levels for blood pressure and serum lipids nationally-representative data from the U.S. population, 2011-2012 NHANES (Centers for Disease Control and Prevention, 2014) and had higher systolic blood pressure and central adiposity and lower HDL-cholesterol than FT-adults from this study. Structural equation models revealed that dietary quality joined term status as a separate and additive contributor to systolic blood pressure, which is consistent with recent findings between poor dietary behaviors, low birth weight and type 2 diabetes (Li et al., 2015). However, new to our study was that dietary quality acted as possible mediator between term status and cholesterol dyslipidemia. Furthermore, higher dietary quality attenuated some of the CVD risk factor associations among preterm adults born with higher medical risk. However, a protective family environment, while benefiting dietary quality for FT-adults [similar to previous research (Savage, Fisher, & Birch, 2007)], was not associated with dietary quality improvements among adults who were born prematurely. Born prematurely may influence responses to the food environment and the development of food preferences. Similar to previous research, PT-adults had less liking for protein foods (Barbieri et al., 2009; Migraine et al., 2013) and wine (Cooke, 2004; Roberts et al., 2013), and greater liking for sweets (Ayres et al., 2012; Barbieri et al., 2009; Silveira et al., 2012) than FT-adults. The PT-adults with lower birth weight also had greater liking for sweets while less liking for fruits/vegetables, consistent with prior findings (Barbieri et al., 2009; Kaseva et al., 2013; Silveira et al., 2012). Contrary to previous findings (Stein et al., 2006), birth weight was not associated with liking for salty foods, which could be explained by differences in the study samples, as we only included
preterm adults with birth weight <1850 grams. New findings from our study were that
PT-adults (especially those with lowest birth weight) reported an overall dietary quality
incongruent with current dietary recommendations for CVD prevention (Eckel et al.,
2013). Individuals born prematurely also may not appropriately self-control these less
healthy food preferences. We found that PT-adults had less dietary restraint than the FT-
adults or norms of college-aged students, which may parallel findings of higher impulsive
eating behaviors among preschoolers born with intrauterine growth restriction (Silveira et
al., 2012).

Lower sensation seeking among PT-adults in our study may further impede
development of healthy eating and related health outcomes. The PT-adults reported less
affinity for sensation seeking (spicy foods, risk taking behaviors) and lower willingness
to try new foods. Adverse neonatal environments (Behrman & Butler, 2007) are
associated with avoidance of novel stimuli (Pliner & Melo, 1997) consistent with PT-
adults reporting lower affinity for sensation seeking/risk behaviors. Although avoidance
of some risky behaviors (smoking, excessive alcohol consumption) decreases CVD risk
(Kajantie & Hovi, 2014), our findings and those of others (Contento, Zybert, & Williams,
2005; Goulet et al., 2008; Moreira, de Almeida, & Sampaio, 2005; Sproesser, Strohhbach,
Schupp, & Renner, 2011) support that PT-adults could achieve healthier diets through
higher cognitive control, self-regulation, early and frequent exposures to novel foods
(Blissett & Fogel, 2013) and novel strategies to improve the sensory characteristics of
healthier foods (Bartoshuk & Klee, 2013; J. E. Hayes & Duffy, 2008; Sharafi, Hayes, &
We observed higher blood pressure, lower HDL-cholesterol and higher waist/hip ratio among PT-adults, which is consistent with early manifestation of blood pressure elevations during childhood (Bonamy, Kallen, & Norman, 2012; de Jong et al., 2012; Poplawska et al., 2012), abnormal lipid profile (Parkinson et al., 2013) and impaired fetal growth relating to central fat distribution (Barbieri et al., 2009; Labayen et al., 2006; Mathai et al., 2013; Thomas et al., 2011). Our findings of additive effects of term status and dietary quality on blood pressure suggest that simultaneous improvement of both prenatal and postnatal factors is needed to manage this CVD risk factor. We did not find a significant relationship between liking for salty foods, term status and blood pressure among PT-adults. Instead overall dietary quality acted as a potential mediator between premature birth and multiple CVD risk factors—dietary quality was lower among PT-adults simultaneously leading to lower HDL-cholesterol and higher TC/HDL-cholesterol, LDL/HDL-cholesterol, and waist to hip ratio. Healthy lifestyle also may protect adults born premature against CVD. Although our findings on the level of physical activity and smoking behaviors at age 23 did not show differences between PT- and FT-adults, the sub-analysis of preterm born adults revealed higher levels of physical activity lowered the risks for CVD by reducing the adiposity levels. Similar to previous research (Kajantie & Hovi, 2014), our results support that adults born prematurely can benefit from early adoption of healthy dietary and lifestyle behaviors to promote health in aging.

The current study provides insights into early-life influences on the relationships between diet and CVD risk in early adulthood. Through cumulative, longitudinal indexes, we capture constructs of family protection, the environmental and medical risks from birth through adolescence. We found no differences between PT- and FT-adults regarding
the cumulative family protection score, which included maternal perception of child
vulnerability, maternal self-esteem, maternal involvement and maternal control style
from birth to adolescence. Surprisingly, the greater family protection was found to only
benefit adults born full term by positively influencing their dietary quality. As parent-
child interactions early in life shape children’s dietary behaviors (Cerro, Zeunert,
Simmer, & Daniels, 2002; Savage et al., 2007), we expected to see a similar benefit of
family protection for PT-adults. Even with similar food environments, PT-adults may still
be at greater dietary risks of CVD due to effects of the prenatal environment to shaping
their dietary preferences.

As fetal programming theory (Barker, Eriksson, Forsen, & Osmond, 2002;
Barker, Osmond, Forsen, Kajantie, & Eriksson, 2007; Sullivan, Hawes, Winchester, &
Miller, 2008) suggests, individuals exposed to adverse prenatal environments develop
compensatory physiological responses to survive that become maladaptive when the
environment alters (Sullivan et al., 2008). Rapid transition from undernourished
intrauterine environment to outside obesogenic environment may result in mismatches
between predicted and actual environments leading to altered food preferences and
dietary behaviors with increased susceptibility to future CVD disease. Heightened
attention to dietary quality might be most important for PT-adults who develop medical
risk. In the present study, PT-adults who had higher cumulative medical risk and higher
dietary quality had 6 mm/Hg lower systolic blood pressure, which could translate to at
least 14% less risk for stroke incidents and 9% reduction in coronary heart disease
mortality (Stamler, 1991).

The study’s limitations and strengths need acknowledgement. Although part of a
longitudinal study, the dietary behavior assessment only was incorporated into Wave VIII (age 23 years) with less information about maternal intake during pregnancy [e.g. flavor exposure in uterine environment (Mennella, Jagnow, & Beauchamp, 2001)] and early nutrition (e.g. breastfeeding), which may link to future cardiovascular health (Singhal, 2006). The lack of dietary intake data during childhood limits the ability to draw conclusions on whether unfavorable dietary behaviors observed among PT-adults were influenced by factors beyond the prenatal environment (e.g. repeated exposure to unhealthy foods at childhood (Kaikkonen et al., 2013; Lioret, McNaughton, Spence, Crawford, & Campbell, 2013; Schwartz, Scholtens, Lalanne, Weenen, & Nicklaus, 2011). Nonetheless at age 23, the liking survey may capture more usual dietary behaviors with less misreporting than food recalls/records or frequency surveys (Duffy et al., 2009; Duffy et al., 2007; Sharafi, Faghri, et al., 2015; Sharafi, Peracchio, et al., 2015). The use of SEM extends beyond traditional regression analysis, which specifies default models, assume measurement occurs without error, and is somewhat inflexible. SEM allows flexibility to incorporate measured variables and latent constructs, while explicitly specifying measurement error to simultaneously determine direct and indirect associations between term status, dietary quality, and CVD risk factors. The FT-adults in the present study showed higher blood pressures than reference values from NHANES. However, similar elevations in blood pressures were reported for Wave IV (24-32 year olds) of National Longitudinal Study of Adolescent Health (Nguyen et al., 2011) in comparison with NHANES 2007-2008. Differences in sample characteristics and setting for blood pressure measurement could explain observed discrepancies with NHANES values. The present study was limited in the ability to provide effects of birth weight on
diet and CVD risk factor relationships in FT-adults (full-term infants with birth weight <2500 g and preterm infants with birth weight >1850 g were not recruited into the study). Finally, the homogeneity improved the internal validity but restricts the generalizability of findings.

In conclusion, this study investigated the simultaneous associations among prematurity status, dietary behaviors and CVD risk factors through structural equation modeling. Young adults who were born prematurely had less healthy dietary behaviors, which in turn associated with elevated biochemical and anthropometric risk factors for CVD. Although the potential impact of the diet-CVD risk factor association is unknown—most preterm adults in large cohort studies have yet to reach age 55, where 86% of first CVD events have occurred (Wald, Simmonds, & Morris, 2011)—the greater survival of former preterm infants into adulthood coupled with obesogenic environments suggests early interventions for individuals born prematurely are warranted to develop healthy eating preferences and habits for promotion of optimal growth and development and for CVD prevention.
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Statement of authors’ contributions to manuscript.

M. S. carried out the analyses, drafted the initial manuscript and all revisions, and approved the final manuscript as submitted; V. B. D developed the dietary assessment protocol, coordinated and supervised the data analysis, critically reviewed the manuscript, and approved the final manuscript as submitted; R. J. M., and S. B. W. coordinated data collection, working with Dr. Sullivan to design preterm risk indexes, reviewed and revised the manuscript, and approved the final manuscript as submitted; T. B. H. supervised the data analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted. M. C. S. designed the data collection, coordinated and supervised the study, developed the preterm risk indexes, critically reviewed the manuscript, and approved the final manuscript as submitted. All authors have read and approved this manuscript submission.
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