LOWEST NEONATAL SERUM SODIUM PREDICTS SODIUM INTAKE IN LOW-BIRTHWEIGHT CHILDREN

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Running head: neonatal serum sodium predicts childhood sodium intake

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Parts of these findings were presented at the Israel Society for Neuroscience, Israel, 2005, and the European Winter Conference on Brain Research, France, 2006.
ABSTRACT

Forty-one children aged 10.5±0.2y (8.0-15.0), born with low birth weight of 1218.2±36.6g (765-1580) were selected from hospital archives on the basis of whether they had received neonatal diuretic treatment, or as healthy matched controls. The children were tested for salt appetite and sweet preference including rating of preferred concentration of salt in tomato soup (and sugar in tea), ratings of oral spray (NaCl and sucrose solutions), intake of salt or sweet snack items, and a food seasoning, liking and dietary questionnaire. Results showed that sodium appetite was not related to neonatal diuretic treatment, birth weight, or gestational age. However, there was a robust inverse correlation (r = -0.445, p<0.005) between reported dietary sodium intake and the neonatal lowest serum sodium level (NLS) recorded for each child, as an index of sodium loss. The relationship of NLS and dietary sodium intake was found in both boys and girls, and in both Arab and Jewish children, despite marked ethnic differences in dietary sources of sodium. Hence, low neonatal serum sodium predicts increased intake of dietary sodium in low birthweight children some 8-15 years later. Taken together with other recent evidence, it is now clear that perinatal sodium loss, from a variety of causes, is a consistent and significant contributor to long term sodium intake.

KEY WORDS

dietary sodium, humans, hyponatremia, neonates, perinatal programming, sodium appetite
INTRODUCTION

The source of individual variation in salt appetite, and why many people ingest an excess of salt, is not known. Early development is considered to be a crucial period for establishing individuality in behavior and may similarly determine individual differences in salt preference. Yet attempts in rats to relate early sodium intake to long-term salt preference have yielded inconsistent results (11,29,37). Similarly, in humans, studies on the determinants of individual variability in salt preference and intake that have concentrated on exposure, acculturation and learning, particularly in infancy and childhood, have not revealed the determinants of individual variability in salt preference (7,18,34) although they have shown how a particular salty food becomes preferred (47).

On the other hand, in rats, long-term increases in salt intake have been found consequent on varied instances of perinatal mineralofluid loss: offspring of dams that during pregnancy were dehydrated, lost sodium, or had their hormones of sodium conservation activated, or rats that were acutely sodium deprived post-natally, all show increased sodium intake in adulthood (4,16,26,29,48).

Similarly, in humans, maternal vomiting during pregnancy increases offspring salt preference, as do childhood vomiting, diarrhea, salt wasting, and electrolyte deficient feeding (9,10,23,27,42).

Much of the human data are based on recall, and it thus remains to be proven that confirmed neonatal sodium deficit increases salt appetite enduringly in humans. In an earlier attempt we tested children who had received neonatal diuretic therapy, and found that 5 children that had received neonatal diuretics had a greater fractional excretion of sodium than their matched controls, suggesting greater sodium intake (30). Here, using data from neonatal medical records, we investigated whether neonatal serum sodium loss might be related to salt appetite in the children 8-15 years later.
Sodium loss in premature infants is defined as hyponatremia if serum sodium falls below 130 mmol/L. It can occur in the first postnatal days because of decreased fluid delivery to the distal nephron diluting segments, often caused by the decreased glomerular filtration rate (GFR) of underdeveloped kidneys. Hyponatremia during the first week of life (early onset) usually reflects free water excess due to increased maternal intake during labor, excess free water administration in the postnatal period, suboptimal sodium intake in oral feeds or parenteral fluids, non-osmotic release of vasopressin in perinatal asphyxia, respiratory distress, bilateral pneumothoraces, intraventricular hemorrhage, or with some medications. Hyponatremia in the latter half of the first month of life (late onset) is most commonly due to excessive renal losses due to high fractional excretion of sodium - particularly in infants born before 28 weeks gestation, inadequate sodium intake, retention of free water from excessive ADH release, renal failure or, less commonly, to edematous disorders (1,15).

Sodium status of the neonates is routinely monitored by drawn blood, or if hyponatremia is indicated.

METHOD

Participants

Forty-one children (table 1) who were born prematurely, were found through the archives of Ha’Emek and Galilee Medical Centers. Participants were told that the purpose of the study was to test whether pre-term birth variables can influence taste preferences and sensitivity to taste. The legal guardians of the participants signed an informed consent form. The study had Helsinki Committee and University of Haifa Human Ethics Committee approval. Prior to testing for salt preference, all participants underwent an examination by a pediatrician and the results were reported to the parents. After the tests, the children were given a toy as a token of gratitude, and parents received 100 Shekels (~20 USD), and traveling expenses were refunded.
The participants were originally selected on the basis of neonatal diuretic treatment or their matched controls that received no diuretic treatment. To maximize the chances of finding diuretic treated neonates, we constrained our search to premature babies born 25 - 34 weeks of gestation, and birth weight of 750-1600 g. Exclusion criteria included children whose medical records suggested a severe congenital or acquired pathology that could lead to a permanent neurological dysfunction, chronic renal disease, intraventricular hemorrhage degree 3-4, neonatal asphyxia, encephalitis, meningitis, periventricular leukomalacia, cerebral edema, steroid treatment, convulsions, renal failure, neonatal jaundice that required exchange transfusion, and neonates large or small for gestational age. Two-hundred and sixteen records matching these criteria were found, of which about 100 were untraceable, and of the remainder 23 that had received neonatal diuretic treatment, and 18 controls that fulfilled the same criteria but had no diuretic treatment, agreed to participate. One additional child who had suffered kidney infection earlier the year of testing was removed from the sample.

We analyzed sodium appetite according to neonatal diuretic treatment (most often because of the chronic lung disease, broncho-pulmonary-dysplasia), and also using each child’s lowest recorded serum sodium (NLS) as an index of sodium loss. Serum sodium is measured routinely in drawn blood from the umbilical artery postnatally, and subsequently from vein, artery, or by heel puncture. Frequency of measurement varies between 2-3 times/day to once every 2-3 days. The NLS was determined by screening all the serum sodium measurements of each infant’s postnatal medical record, and selecting the lowest.
TABLE 1
participant characteristics and group sizes used in the analyses

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>mean±SEM (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal data</strong></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>birth weight (g)</td>
<td></td>
<td>1218.2±36.6 (765-1580)</td>
</tr>
<tr>
<td>gestational age (weeks)</td>
<td></td>
<td>29.5±0.4 (25-34)</td>
</tr>
<tr>
<td>age of lowest serum Na⁺ (d)</td>
<td></td>
<td>9.7±1.6 (1-42)</td>
</tr>
<tr>
<td>release weight (g)</td>
<td></td>
<td>2268.3±31.6 (2035-2835)</td>
</tr>
<tr>
<td><strong>Childhood data</strong></td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>age at testing (y)</td>
<td></td>
<td>10.5±0.2 (8.0 -15.0)</td>
</tr>
<tr>
<td>BMI at testing</td>
<td></td>
<td>17.9±0.5 (13.4-27.2)</td>
</tr>
<tr>
<td>Arabs</td>
<td>21</td>
<td>boys 14 girls 7</td>
</tr>
<tr>
<td>Jews</td>
<td>20</td>
<td>boys 11 girls 9</td>
</tr>
<tr>
<td>girls</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>boys</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

**Procedure**

The children, with their parents, were invited to be tested in a room in the same wards where they had been as neonates. The children were asked to avoid eating and drinking beverages, other than water, for two hours before arrival. They underwent a pediatric physical examination. Blood and urine samples to assess sodium intake were requested, but too few participants agreed for meaningful analyses. To estimate sodium appetite, participants were then tested for preferred concentration of salt in soup and sugar in tea, followed by the test with the oral sprays of NaCl and sucrose. Between the taste tests, the children and the escorting parent(s) were interviewed in order to complete the dietary, seasoning, and preference questionnaire. After finishing the taste tests, while still completing the questionnaire, the participants were invited to eat freely from salty and sweet snacks (23,27).

All testing was carried out by 5 laboratory researchers trained in the use of the tests, and administrating the tests in teams of 3.
Behavioral tests

Preferred concentration of NaCl in soup and sugar in tea:

Tomato soup (2mg Na⁺/100g) was prepared by diluting 1 part of unsalted tomato paste concentrate (22BX, 20mg Na⁺/100g) with nine parts of boiled water. Tea was prepared with a 3 gr. tea bag in one liter of boiled water. The soup and tea were prepared freshly before each test session, in the ward kitchen and kept in vacuum flasks at ~45°C (23,46).

Participants were presented with two 200 ml cups of tomato soup, one unsalted and one with 3.3% (w/w) NaCl, they were asked to taste the soup in both cups and then they were provided with a third cup, into which the experimenter poured one-half of the unsalted soup. Then, using a 5 ml teaspoon, they were asked to add salted soup to the third cup and taste it until they deemed the mixture most "tasty". The salt concentration of the mixture was determined by weighing the cups. Preference for sucrose in tea was similarly determined, using tea with 20% (w/w) sucrose.

Ratings of sweet and salty solutions in oral sprays:

For rating intensity and preference for salt solution, NaCl was diluted with bottled water from 2.56M to 6 concentrations by 1:3 steps down to a concentration of 0.0035M. Six concentrations of sucrose were prepared from 135 g/l by 1:3 step dilution to the lowest concentration of 0.56 g/l. The experimenter sprayed 0.29 ml of each taste concentration in pseudo-counterbalanced randomized orders (avoiding sequential concentrations) onto the participant’s tongue. Using visual analogue scales (VAS), participants rated each concentration for taste intensity (“how strong is the taste?” – in Hebrew) anchored by “don’t feel anything” and “very strong”, and for hedonics (“how tasty is it?”) anchored by “bad taste” and “very tasty”. The mean of the three highest concentrations (lower concentrations were unreliably discriminated) served for scoring for the salt appetite determination (below) (We are grateful to Burt M Slotnick for suggesting this method).
**Sweet and salty snacks:**

Participants were invited to eat freely from 2 familiar commercial salty (890 and 780 mg Na\(^+\) per 100g) and sweet snack items (120.5 and 146 mg Na\(^+\) per 100g) presented on separate saucers in unwrapped bite-size morsels. The number of morsels eaten was scored.

**Questionnaire**

The investigator interviewed each child with its parent(s) using a questionnaire covering 65 food items of the common Israeli diet (23,27). The questionnaire provided three scores for the analyses:

A. Dietary intakes

Participants were asked about their weekly frequency of consumption, and quantities consumed, of food items. These were used to calculate NaCl, carbohydrate, sweet carbohydrate, fat and protein content of their daily diet using the Ministry of Health nutritional values and portion size tables (36).

B. Salting and sweetening:

They were asked how much sugar and salt (or pepper, oil/butter, etc) they add to season relevant food items (scored on a three-level scale).

C. food preference (liking)

Participants were asked to rate “how much they like” each food item in the questionnaire on a 5 point scale anchored at the ends with “greatly dislike” and “like very much”.

**Salt Appetite**

Salt appetite was operationally defined as the unweighted mean of the above 5 measures (soup, oral spray hedonics, salt snacks, dietary Na\(^+\), salting. Each score was transformed by dividing it by the highest score of the measure). Equivalent sweet preference measures were calculated (tea, oral spray hedonics, sweet snacks, dietary sweet carbohydrates, sweetening. 23,27).
Statistical analysis

The effect of neonatal diuretic treatment on sodium appetite and sweet preference was analyzed by ANOVA. In addition, correlational analysis (Spearman) was used to examine the relationship of neonatal sodium loss to long-term sodium appetite, using each child’s lowest recorded neonatal serum sodium (NLS). Measures of salt preference, individually scored and combined into “salt appetite” were correlated with NLS using SPSS. Correlation was employed to discover which food items correlated with NLS. Stepwise regression analysis was employed to determine predictors of sodium intake and sweet preference.

Alpha was fixed at 0.05 and SEM is the measure of variability throughout the report.

RESULTS

Effect of neonatal diuretic therapy on salt appetite and NLS

Diuretic treatment did not influence any of the measures of salt preference (except for a trend for greater intake of salt snacks, 25.1±5.0 vs. 12.8±2.5 morsels, p=0.51). Children who received diuretic therapy had lower NLS (diuretic-treated NLS 128.7±0.9 vs. 133.2±1.0 mEq/L for non-treated, p<0.005) as well as a higher maximal serum sodium (respectively 145.4±1.0 vs. 141.1±1.1 mEq/L, p<0.01). However, diuretic administration was not directly related to NLS, since in the 23 neonates who received it, of 84 diuretic administrations, only 5 dates coincided with the NLS and one more was the day before. This is not unexpected, since diuretic administration is accompanied by electrolyte infusion specifically to prevent hyponatremia.

Correlations of salt appetite and sweet preference with NLS

The distribution of age of NLS is presented in figure 1. It shows that NLS occurs most frequently in the first 2 weeks postnatal (figure 1). In the 14 participants with severe hyponatremia (<130 mEq/L (15), figure 1), its incidence (in days) for each participant correlated with NLS, r=-0.782, p<0.005, so that the single measurement of NLS is a good index of cumulative hyponatremia.
Moreover, in this group with severe hyponatremia, intake of salty snacks was greater than in all the other participants (n=17), 30.1±6.6 morsels vs. 14.3±2.9, p<0.05, and dietary sodium intake was substantially higher at 4515±310 mg/day vs. 3307±248, p=0.0054.

Table 2 presents the correlations between NLS and tests of salt and sweet preference. Only dietary sodium intake correlated significantly with NLS. Figure 2 shows this correlation by ethnicity and gender.

### TABLE 2
Correlations of salt appetite and sweet preference with NLS

<table>
<thead>
<tr>
<th>Measure</th>
<th>n=41</th>
</tr>
</thead>
<tbody>
<tr>
<td>adding salt</td>
<td>0.085</td>
</tr>
<tr>
<td>dietary Na(^+)</td>
<td>-0.445*</td>
</tr>
<tr>
<td>salty snacks</td>
<td>-0.269</td>
</tr>
<tr>
<td>salting soup</td>
<td>0.015</td>
</tr>
<tr>
<td>hedonic salty spray</td>
<td>0.092</td>
</tr>
<tr>
<td>salt appetite</td>
<td>-0.097</td>
</tr>
<tr>
<td>adding sugar</td>
<td>0.015</td>
</tr>
<tr>
<td>dietary sweet CHO(^1)</td>
<td>0.038</td>
</tr>
<tr>
<td>sweet snacks</td>
<td>-0.186</td>
</tr>
<tr>
<td>sweetening tea</td>
<td>0.190</td>
</tr>
<tr>
<td>hedonic sweet spray</td>
<td>0.179</td>
</tr>
<tr>
<td>sweet preference</td>
<td>0.012</td>
</tr>
</tbody>
</table>

\*p<0.005, \(^1\)CHO – carbohydrates.
Table 3 presents the correlation of NLS with dietary macronutrients and electrolytes. Only sodium correlated significantly with NLS.

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>energy (Kc)</td>
<td>-0.198</td>
</tr>
<tr>
<td>proteins (g)</td>
<td>-0.191</td>
</tr>
<tr>
<td>fat (g.)</td>
<td>-0.177</td>
</tr>
<tr>
<td>CHO (g.)</td>
<td>-0.229</td>
</tr>
<tr>
<td>calcium (mg)</td>
<td>0.065</td>
</tr>
<tr>
<td>sodium (mg)</td>
<td>-0.445*</td>
</tr>
<tr>
<td>potassium (mg)</td>
<td>-0.201</td>
</tr>
<tr>
<td>dietary sweet CHO (g)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

*p<0.005

NLS also correlated with dietary sodium standardized for caloric intake (r=-0.368, p<0.02).

Comparisons of children with low and high NLS.

To examine the influence of NLS by group comparisons, we selected children with the lowest NLS (120-125 mEq/L, n=6) and the highest (135-140 mEq/L, n=7). These revealed that the low NLS children ingested 4743±422 mg sodium/day, while the high NLS children ingested 3030±500, a difference of 1,713±667 mg/day (p<0.05). The low and high NLS children differed,
respectively, on gestational age 27.7±0.7 and 31.0±1.0, p<0.05, and substantially on childhood body weight, 36.9±3.6 and 27.8±2.0 kg, and BMI, 20.0±1.4 and 15.1±0.6 (p’s<0.005) but not on height, 136.7±4.3 and 135.3±2.8. They did not differ significantly on any other intake, birth, neonatal, or childhood parameters.

Boys had a greater salt appetite than girls, 0.398±0.030 and 0.308±0.030, p<0.05.

**Dietary sources of sodium**

Dietary sodium intake was 3720±212 mg/d (1508-6875). Table 4 presents the food items that correlated with NLS, by ethnicity and gender.

<table>
<thead>
<tr>
<th>Food item</th>
<th>Na⁺ mg/100g</th>
<th>all n=41</th>
<th>Arabs n=21</th>
<th>Jews n=21</th>
<th>boys n=25</th>
<th>Girls n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>popcorn</td>
<td>884</td>
<td>-0.244</td>
<td>0.038</td>
<td>-0.497*</td>
<td>-0.339</td>
<td>-0.136</td>
</tr>
<tr>
<td>pita</td>
<td>650</td>
<td>-0.309*</td>
<td>-0.544*</td>
<td>-0.144</td>
<td>-0.287</td>
<td>-0.328</td>
</tr>
<tr>
<td>yellow cheese</td>
<td>630</td>
<td>-0.158</td>
<td>-0.014</td>
<td>-0.552*</td>
<td>-0.101</td>
<td>-0.232</td>
</tr>
<tr>
<td>tinned tuna</td>
<td>520</td>
<td>-0.265</td>
<td>-0.097</td>
<td>-0.468*</td>
<td>-0.149</td>
<td>-0.429</td>
</tr>
<tr>
<td>white cheese 5% fat</td>
<td>400</td>
<td>-0.150</td>
<td>0.046</td>
<td>-0.460*</td>
<td>-0.034</td>
<td>-0.234</td>
</tr>
<tr>
<td>tehine</td>
<td>400</td>
<td>-0.167</td>
<td>0.060</td>
<td>-0.600**</td>
<td>-0.075</td>
<td>-0.302</td>
</tr>
<tr>
<td>instant soup</td>
<td>400</td>
<td>-0.337*</td>
<td>-0.306</td>
<td>-0.430</td>
<td>-0.120</td>
<td>-0.670**</td>
</tr>
<tr>
<td>tinned vegetables</td>
<td>395</td>
<td>-0.301</td>
<td>-0.139</td>
<td>-0.453*</td>
<td>-0.463*</td>
<td>-0.023</td>
</tr>
<tr>
<td>yoghurt</td>
<td>130</td>
<td>-0.320*</td>
<td>-0.109</td>
<td>-0.478*</td>
<td>-0.197</td>
<td>-0.558*</td>
</tr>
<tr>
<td>Boiled egg</td>
<td>126</td>
<td>-0.138</td>
<td>-0.169</td>
<td>-0.509*</td>
<td>0.074</td>
<td>-0.518*</td>
</tr>
<tr>
<td>Boiled fish</td>
<td>78</td>
<td>0.238</td>
<td>0.166</td>
<td>0.182</td>
<td>0.468*</td>
<td>-0.102</td>
</tr>
<tr>
<td>ice cream</td>
<td>57</td>
<td>0.344*</td>
<td>0.436*</td>
<td>0.435</td>
<td>0.348</td>
<td>0.317</td>
</tr>
<tr>
<td>milk</td>
<td>48</td>
<td>-0.228</td>
<td>0.065</td>
<td>-0.560*</td>
<td>-0.45</td>
<td>-0.550*</td>
</tr>
<tr>
<td>Boiled potatoes¹</td>
<td>5</td>
<td>-0.288</td>
<td>-0.497*</td>
<td>-0.146</td>
<td>-0.259</td>
<td>-0.347</td>
</tr>
</tbody>
</table>

¹unsalted value
* p<0.05, **p<0.005

Table 4 shows that dietary sodium intake correlated with NLS for different foods in the two ethnic groups. Analyses of sodium intake for each food item by ethnicity and gender showed that...
sodium intake of 18 foods differed by ethnicity (table 5). There were marked ethnic differences in
sources of sodium in the two diets, e.g. Arab children obtained much of their sodium from their
staple pita bread and bread rolls, whilst Jewish children obtained it from bread and home-made
soups (table 5). In addition to pita, which accounted for a large portion of sodium intake, intake
of hummus, popcorn and boiled fish both correlated with NLS and differed in the two ethnic
diets. Interestingly, ice cream, a low sodium food, was avoided by the neonatal hyponatremics.
### TABLE 5
Differing dietary sodium sources by ethnicity

<table>
<thead>
<tr>
<th>food item</th>
<th>Na⁺ content mg/100g</th>
<th>Arabs n=21</th>
<th>Jews n=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>pita</td>
<td>650</td>
<td>1156.7±96.5***</td>
<td>189.4±46.5</td>
</tr>
<tr>
<td>bread</td>
<td>650</td>
<td>13.3±6.3</td>
<td>344.0±80.8***</td>
</tr>
<tr>
<td>salt snacks</td>
<td>600</td>
<td>332.7±61.4**</td>
<td>141.4±29.7</td>
</tr>
<tr>
<td>Corn flakes &amp; milk</td>
<td>250</td>
<td>81.6±28.1</td>
<td>205.0±48.5*</td>
</tr>
<tr>
<td>home made soup³</td>
<td>200</td>
<td>68.0±17.4</td>
<td>181.3±47.6*</td>
</tr>
<tr>
<td>bread rolls</td>
<td>360</td>
<td>180.2±36.8**</td>
<td>65.8±20.3</td>
</tr>
<tr>
<td>hummus</td>
<td>430</td>
<td>177.7±52.6*</td>
<td>47.6±12.3</td>
</tr>
<tr>
<td>Labane²</td>
<td>500</td>
<td>149.7±33.6***</td>
<td>22.9±12.9</td>
</tr>
<tr>
<td>kebab, hamburger</td>
<td>611</td>
<td>110.8±22.7**</td>
<td>31.2±8.7</td>
</tr>
<tr>
<td>vegetarian schnitzel</td>
<td>650</td>
<td>4.6±3.7</td>
<td>96.3±40.0*</td>
</tr>
<tr>
<td>popcorn</td>
<td>884</td>
<td>29.8±11.0</td>
<td>85.2±23.0*</td>
</tr>
<tr>
<td>tehine</td>
<td>400</td>
<td>60.0±16.6**</td>
<td>3.3±1.8</td>
</tr>
<tr>
<td>5% fat white cheese</td>
<td>400</td>
<td>10.7±6.1</td>
<td>48.8±14.1*</td>
</tr>
</tbody>
</table>

Food items that contributed different amounts of Na⁺ (mg/day), and macronutrient and electrolyte consumption in diets of Arab & Jewish children (±SE).

* p<0.05, **p<0.01, ***p<0.001, greater than for children of other ethnic group.

1 Arranged in descending order of Na⁺ contribution. Five additional foods that differed are not included in the table because their Na⁺ contribution was negligible.

2 soured goat's milk.

3 Home-made soups usually include commercial cubes of powdered chicken or vegetable stock, with a dry sodium content of 450mg/g.
Sodium intake was substantially higher in Arab children, probably because dietary intakes of energy, fat, and carbohydrates were also greater in Arab children (table 5). There were no significant gender differences, or interactions with ethnicity, on any dietary measures or BMI, indicating that boys and girls showed the phenomenon of the relationship of NLS with dietary sodium similarly.

*Liking of foods and NLS*

NLS correlated with liking of only one food item (tuna, among Jewish children, r=-0.627, p<0.01). This was also one of the items whose intake correlated with NLS in Jewish children (table 4).

*Dietary sodium and neonatal parameters*

NLS correlated with gestational age (r=0.521, p<0.001) and birth weight (r=0.357, p<0.05), which also correlated with dietary sodium (r=-0.357, p<0.05). Stepwise multiple regression of sodium consumption by birth weight, gestational age, frequency of neonatal diuretic administration, and NLS was significant (F(4,18)=4.1, p<0.05), but NLS was the only significant predictor of dietary sodium consumption (β= -0.770, p<0.005).

There was a correlation of NLS with children’s current BMI, r= -0.311, (p<0.05), but it dissipated when controlled for the above variables.

*Sodium appetite and childhood vomiting, diarrhea and dehydration*

The frequency of these scores was too low for meaningful analysis (6-9 children, mostly scoring just one episode, in the sample of 42).

**DISCUSSION**

Reported dietary sodium consumption in childhood was predicted by neonatal lowest serum sodium (NLS). NLS occurred most frequently in the first 2 weeks postnatal, consistent with the predominant occurrence of hyponatremia in this period (1). A regression model showed that
gestational age, birth weight, and frequency of diuretic therapy, were not predictors of childhood sodium intake. Neonatal lowest serum sodium predicted dietary sodium intake in both Arab and Jewish children, and in both boys and girls. This suggests an influence of NLS on later sodium intake, and indeed, children with lower neonatal sodium had a greater calculated sodium content in their diet, and reported greater intake of sodium-rich foods such as popcorn, pita, yellow cheese, tinned tuna, white cheese, tehine, instant soup and tinned vegetables. These are common foods in the Israeli diet, and it would seem possible for a child 8-15 years-old to adjust its intake within the constraints of the parental served diet.

There was no relationship of NLS with intake of sweet foods (other than ice-cream) suggesting a specific relationship to salt intake. The positive correlation of NLS with intake of ice-cream as a low-sodium food is entirely consistent with the negative correlation of NLS with intake of high-sodium foods.

The correlation between NLS and childhood dietary sodium intake was evident in both Arab and Jewish children. Tellingly, different foods supplied the sodium that correlated with NLS in the two ethnic diets, suggesting that the increased dietary sodium intake is regulated independently of dietary composition. It should be noted that this correlation also implies that children who had high neonatal minimal serum sodium had a lower dietary sodium intake, although we only found one food (ice cream) that correlated positively and significantly with NLS.

There were no gender differences in dietary sodium consumption, although boys scored higher on sodium appetite.

Other than an indication of increased intake of salt snacks, we found no relationship of NLS with preference for salt per se. This is reminiscent of our previous finding with children treated neonatally with diuretics who showed no preference for salt, although fractional excretion of sodium measured in 5 children was almost twice that of matched controls, suggesting higher consumption of sodium (30). Explaining increased sodium intake without increased preference is
awkward (51). The sodium ingested with industrially prepared foods such as the above has been termed "insensible" sodium intake because the sodium is not tasted (33,42), so that the post-ingestive effects of sodium might condition such preferences. Indeed, we have demonstrated such conditioning to untasted sodium, but that was related to presumed sodium need (49), for which there is no evidence in these children.

Clearly, the source of the preference for these sodium-rich foods was the neonatal blood sodium level, its causes or sequelae, since other gestational and birth parameters were excluded. Others have shown that in healthy neonates 2-4 days old, intake of a test NaCl solution is correlated to birthweight (and blood pressure (53)). By 2 months this is reversed to a negative correlation, which may persist to 3-4y (45). Since birthweight and later body weight are negatively correlated (6,17,25,39), as we have shown here too, these might be complimentary findings, sodium appetite correlating positively with birthweight, but then, as the low birthweight infants get heavier than their peers (25), the correlation reverses. The relationship to NLS remains to be clarified, since we show here that sodium consumption at 8-15 years is better explained by NLS than birthweight. The contribution of maternal vomiting needs to be considered too, since it relates to both reduced birthweight (54) increased sodium appetite in the offspring (9,10,27), and to NaCl gustatory thresholds and blood pressure in adolescents (32).

The increased dietary sodium intake following upon low neonatal serum sodium is broadly consistent with accumulating evidence that perinatal mineralofluid loss is a determinant of long-term sodium appetite. Maternal vomiting during gestation, infantile diuresis, diarrhea, vomiting, and inadequate infant-formula electrolytes, have all been linked to long-term increased sodium appetite in humans (9,10,23,27,30,44) and are consistent with findings in animals (4,16,26,29,48).

One possible mechanism known from rats is that dietary sodium restriction instituted during pre- and postnatal development reduces the size of adult taste buds, alters cell dynamics, induces
gross changes in dendritic length and number and, as little as 9, or even 3 days of sodium restriction, increases the volume of chorda tympani and IX nerve terminal fields in the brainstem. It has been suggested that such comprehensive changes might alter taste-related behaviors, including sodium appetite (21,24,35,43).

Another possible mechanism that can also have long term effects is perturbation of the developing renin-angiotensin-aldosterone system leading to greater neonatal salt loss and long-term increases in sodium appetite (1,12,23,31,40,41). Preterm infants of less than 32-35 weeks gestation or less than 1,500g at birth have obligate high renal and intestinal sodium losses during the first fortnight of life, leading to cumulative negative sodium balance in most, and hyponatremia in many (1,20). The neonates in our study were 29.5±0.4 (25-34) weeks of gestation and 1218±37g (765-1580) at birth, well within the risk range, and indeed many were hyponatremic (figure 1). It has long been recognized that sodium depletion enlists the renin-angiotensin-aldosterone system, primarily central but also peripheral, to increase sodium intake, and the same system may also program the long-term increase in sodium appetite (12,22,31,40,41,50) even if activated in utero (4,16,27,48).

It has been proposed that such perinatal alterations may be adaptive, specifically in increasing sodium appetite (12,14,23,29) or, more generally, to meet cardiovascular and hydrational challenges, occasionally referred to as ‘programming’ or ‘imprinting’ (3,5,6,32,38).

Infant sodium deficiency has long-term adverse effects on the child’s development and health and in preterm neonates has been linked to long-term and wide-ranging motor, audioneurological, growth, cognitive, and affective impairments (1,13,19,20). It has been suggested that sodium plays an important role in early growth by stimulating protein synthesis and cell proliferation and mass, so that deprivation of NaCl in these early developmental stages leads to reduced body and brain weight (19). Conversely, the restorative capacity of sodium is well known and in preterm neonates sodium supplementation is routinely practiced, and has been found to improve
performance in tests of IQ, motor function, memory and language skill (1), and prevent the accelerated weight gain that typifies preterm and low birthweight children (5,6,17,19,25,39). In fact, in our extremes of NLS, children with the lowest NLS were 30% heavier than those with NLS within the norm of 135-140 mEq/L, possibly because of inadequate sodium supplementation in the late 1980’s when our participants were born. Possibly too, marginally compromised renal function (52) may increase sodium loss and consequent compensatory intake in these children (23).

The findings suggest that neonatal hyponatremia predicts increased intake of dietary sodium in low birthweight children. In our study, the effects were evident in a relatively small sample, and were portentous - the children who 8-15 years earlier were most hyponatremic, ingested ~1,700 mg more sodium per day, and weighed some 30% more than their peers, both independent risk factors for cardiovascular disease, and hypertension in salt-sensitive individuals (2,8). Whether similar relationships to neonatal serum sodium pertain to normal weight and term neonates requires urgent pursuit, but these findings accentuate the importance of monitoring and balancing sodium levels in premature babies.

Taken together with other recent evidence (4,9,10,16,23,26,27,30,44,48), it is now clear that perinatal sodium loss, from a variety of causes, is a consistent and significant contributor to long term sodium intake.

It remains that neonatal serum sodium is a marker of future sodium intake, and clinicians might wish to appraise families of neonates with low serum sodium of the risks for early increased sodium intake and corpulence, their recognition, management, and implications.
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FIGURE LEGENDS

Figure 1. Distribution of neonatal minimal serum sodium (NLS) by age and severity.

Figure 2. Correlations of NLS and dietary sodium in children by ethnicity (left) and gender (right). Arabs and boys solid symbols and continuous lines. Jews and girls: hollow symbols and dashes. Correlations: Arabs $r=-0.333$ (n.s., Without outlier: $-0.470^*$); Jews $r=-0.520^*$; boys $r=-0.549^*$; girls $r=-0.400^*$. *$p<0.05$. cf table 1 for n’s.