Sex differences in the relationship of dietary fatty acids to cognitive measures in American children

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Because the first neurons evolved in an environment high in the $n-3$ (omega-3) fatty acid docosahexaenoic acid (DHA), this fatty acid became a major component of neural structure and function and makes up 10% of the dry weight of the human brain. Since $n-3$ fatty acids must come from the diet, this suggests a possible positive role for dietary $n-3$ fatty acids in cognition and a possible negative role for $n-6$ fatty acids, which compete with $n-3$ for access to critical enzymes. Because human females must provide DHA for the growth of the unusually large brains of their offspring from maternal fat stored during childhood, their need for DHA is especially great. We used stepwise regression to determine whether particular dietary fatty acids and other nutrients were related to cognitive performance in over 4000 American children aged 6–16 from the Third National Health and Nutrition Examination Survey; a variety of possible biological, social, and environmental risk factors were statistically controlled. In this context the only dietary factors related to cognitive performance were $n-3$ and $n-6$ fatty acids. Dietary $n-3$ fatty acids were positively related to cognitive test scores in male and female children, while $n-6$ showed the reverse relationship, significantly so in females. In female children the positive effects of $n-3$ intake were twice as strong as in males and exceeded the negative effects of lead exposure. This suggests that increasing dietary intake of $n-3$ and decreasing $n-6$ fatty acids may have cognitive benefits in children, especially in females.

Keywords: essential fatty acids, DHA, cognition, diet, brain, sex differences, evolution

INTRODUCTION

The $n-3$ (also called omega-3) long-chain fatty acid docosahexaenoic acid (DHA, 22:6n−3), with a 22-carbon chain and six double bonds, comprises about 10% of the dry weight of the human brain (Svennerholm, 1968; Rapoport, 2003). Animal studies have shown that DHA readily crosses the blood/brain barrier (Ouellet et al., 2009) and plays a critical positive role in all aspects of neuronal growth, synaptic connections, and functioning (Cockburn, 1994; Jamieson et al., 1999; Salem et al., 2001; Chang et al., 2009). This includes roles in regulating the activity of Na + K + ATPase in the neural membrane (Bourre et al., 1989; Turner et al., 2003; Kumosani et al., 2011), neuron size (Ahmad et al., 2002), neurogenesis (Auestad and Innis, 2000; Coti Bertrand et al., 2006; Beltz et al., 2007; Novak et al., 2008; Da Costa et al., 2009; Dagai et al., 2009; He et al., 2009), neurite growth (Calderon and Kim, 2004; Sakamoto et al., 2007; Liu et al., 2008; Novak et al., 2008; Cao et al., 2009), synapse formation and function (Yoshida et al., 1997; Cansev and Wurtman, 2007; Wu et al., 2008; Cao et al., 2009; Wurtman et al., 2009), neuronal integrity and vitality (Issa et al., 2006; Mukherjee et al., 2007; Niemoller et al., 2009), gene expression in the brain (Kitajka et al., 2002), brain glucose transport (Pifferi et al., 2007), cognitive development (Heinemann and Bauer, 2006; Bongiovanni et al., 2007; Coluccia et al., 2009), and learning ability (Bourre et al., 1989; Yoshida et al., 1997; Greiner et al., 1999; Salem et al., 2001; Takeuchi et al., 2002; Shirai and

Suzuki, 2004; Garcia-Calatayud et al., 2005; Lim et al., 2005; Chung et al., 2008; Holguin et al., 2008; Fedorova et al., 2009; He et al., 2009; Hooijmans et al., 2009; Jiang et al., 2009).

Because animals lack the enzyme required to make an $n-3$ double bond, at least the basal $n-3$ fatty acid, alpha-linolenic acid (ALA, 18:3n−3), must be obtained from their diets. Mammals can convert ALA to eicosapentaenoic EPA, 20:5n−3), and can subsequently convert EPA to docosapentaenoic (DPA, 22:5n−3) and then to DHA, though conversion efficiency is quite low and capacity limited, especially for EPA to DHA (Pawlosky et al., 2001). As cited above, animal studies show that a deficiency of dietary $n-3$ fatty acids leads to a decrease in neuronal size and synapse number and impaired learning ability. Many studies in human infants have shown that levels of DHA in the maternal diet or blood during pregnancy and in maternal milk or formula are positively related to cognitive and visual development in infants, as reviewed by McCann and Ames (2005); Eilander et al. (2007); Innis (2009); Ryan et al. (2010); and Schuchardt et al. (2010). Studies involving the $n-3$ content of the maternal diet may underestimate the effect of DHA, because most DHA delivered by a mother to her fetus or nursing infant derives from her fat stores rather than current intake (Sauerwald et al., 2000).

Most studies relating the level of $n-3$ fatty acids in the diet or blood to cognitive measures in older children have also found a positive relationship, including studies in Italy (Agostoni et al.,

1997), Scotland (Whalley et al., 2004), Maryland (Ryan and Nelson, 2008), Finland (Aberg et al., 2009), Alabama (Neggers et al., 2009), and Wales (Kirby et al., 2010), though a Dutch study did not (De Groot et al., 2007). Two studies in which children were provided with short-term supplemental dietary $n-3$ found a positive effect on cognitive measures (Richardson and Montgomery, 2005; Dalton et al., 2009) and two did not (Osendarp et al., 2007; Kennedy et al., 2009). None of these studies have considered sex differences which, for reasons we will outline below, are to be expected.

EVOLUTIONARY BACKGROUND FOR THE ROLE OF DHA IN THE HUMAN BRAIN

The reliance of human and other mammalian brains on the neuronal functions of DHA appears to be the result of a very ancient evolutionary contingency. Though DHA is now a relatively scarce and limiting resource for the development of large brains in terrestrial environments, neurons first evolved in an aquatic environment where high levels of DHA were readily available. The first links in this chain of contingency apparently reach back more than 3 billion years.

Ancient cyanobacteria evolved the ability to synthesize $n-3$ ALA for incorporation into the thylakoid membrane where it plays an essential role in photosynthesis – as it does today in the chloroplasts of all green plants. Dinoflagellates and certain cyanobacteria and algae subsequently evolved a metabolic pathway to efficiently convert ALA to DHA using the enzyme delta-4-desaturase, and these phytoplankton are still the source of DHA for all aquatic animal life. Fossilized acritarchs suggest that dinoflagellates may have evolved more than 3 billion years ago (Javaux et al., 2010).

The first neurons evolved in Precambrian cnidarians feeding on dinoflagellates and other phytoplankton rich in DHA (Nichols et al., 2003; Putnam et al., 2007); hence neurons could evolve a design that was dependent on substantial supplies of DHA. When larger and more elaborate brains evolved in marine vertebrates, their neurons could continue to rely on large amounts of DHA because the phytoplankton producing this long-chain polyunsaturated fatty acid also lay at the base of their food chain. (DHA's function is not limited to the vertebrate nervous system; it also plays important roles in muscles, blood, and mitochondria.)

Marine arthropods also have a diet rich in DHA, but when exclusively terrestrial arthropods first colonized the land, they were cut off from the DHA supplied by phytoplankton and had minimal ability to synthesize longer-chain $n-3$. Although their bodies have significant amounts of ALA obtained from plants, their nervous systems contain little or no DHA (Jerde et al., 1975; Fontaneto et al., 2011); instead they use mainly ALA (Stark et al., 1993; Shanker et al., 2006). Their inability to convert alpha-linolenic to DHA may limit the complexity of their nervous systems. Reptiles subsequently evolved this conversion ability, although their synthetic pathway differs from that of phytoplankton (lacking delta-4 desaturase), and is very much less efficient. Although allometrically small reptilian brains have some DHA, the proportion of DHA is quite low compared with mammalian brains (Mitchell et al., 2007), and their limited $n-3$ supply may have similarly constrained the growth and hence the evolution of a more complex nervous system.

The evolution of endothermy in mammals greatly increased caloric requirements, and the concomitant 10-fold increase in consumption of plants and/or insects provided much larger amounts of ALA, permitting the synthesis of larger amounts of DHA despite the inefficiency of this process in terrestrial animals. These higher levels of dietary $n-3$ allowed for a considerable expansion of the mammalian brain, which is not only allometrically much larger than a reptile brain but also contains a much higher proportion of DHA (Mitchell et al., 2007). However, mammals still have a lower proportion than fish (Stoknes et al., 2004; USDA, 2011). Higher DHA levels in mammalian mitochondrial membranes also facilitated endothermic metabolism (Brand et al., 1991, 1994; Hulbert, 2007). Meanwhile, the evolution and diversification of flowering plants led to increases in the $n-3$ content of terrestrial plants, especially in their fruits, nuts, and seeds, and permitted the co-evolution of many new species of herbivorous insects with high levels of ALA.

The first primates were insectivores occupying a nocturnal, arboreal niche, and their enhanced feeding skills and diet permitted the further expansion of the primate brain. (Chimpanzee females continue to invest considerable amounts of time feeding on insects as shown by McGrew, 1979.) Frugivorous primates also obtain substantial amounts of insects in the fruit they eat (Redford et al., 1984) as well as higher concentrations of $n-3$ in nuts and seeds. Folivorous primates, like gorillas, have relatively smaller brains compared to frugivores (Clutton-Brock and Harvey, 1980; Harvey et al., 1980), and must still ingest a large volume of plants to provide the necessary $n-3$.

As the hominid brain expanded to a size seven times larger than expected from the brain:body size relationship in mammals, the need for $n-3$ and DHA increased proportionately. Because human synthesis of DHA from ALA remains very limited, like that of other terrestrial animals, sources of preformed DHA in the diet are important. Potential sources include the meat, organs, and eggs of herbivores and birds, and especially flesh from aquatic animals, which provides larger amounts of DHA. Some have argued that exploitation of aquatic nutritional resources was essential for the evolution of the large hominid brain (Broadhurst et al., 2002), and there is evidence for significant amounts of aquatic foods in hominid diets from two million years ago (Braun et al., 2010; Stewart, 2010).

In order to grow their very large brains, human fetuses, and nursing infants require much larger amounts of DHA than can be reliably obtained from maternal daily intake, and most of the DHA they receive comes from maternal fat stores. Studies using radioisotope-labeled fatty acids show that approximately 80% of the DHA and other essential long-chain fatty acids provided in human milk come from maternal fat rather than from the current diet (Sauerwald et al., 2000). These fatty acids are stored mainly in women's gluteofemoral fat, and these depots are protected except during the third trimester and lactation when their fatty acids are mobilized (Lassek and Gaulin, 2006). Because men do not make these physiological investments in offspring, women's need for these fatty acids greatly exceeds that of men, a fact that probably explains the unique human sex difference in body fat.

There is no facilitated transport of DHA into adipose, so the proportion of DHA in fat stores depends on the concentration

of DHA in the blood. Because this concentration is relatively low compared with other fatty acids, the percentage in adipose is also relatively low (0.2–0.3%). Developing human females must therefore have substantial amounts of adipose tissue in order to store sufficient amounts of DHA to support the growth of large brains in their children. In a study of Dutch children, female fat increased from 14.8 to 25.5% of body weight during puberty, while male fat decreased from 10.5 to 9.3% (Boot et al., 1997). In a sample of young American women, there was a mean of 16.2 kg of adipose tissue at the end of puberty (Lassek and Gaulin, 2006). Assuming a DHA percentage of 0.2%, this amount of adipose would contain 32 g of DHA which would become available when adipose is mobilized during late pregnancy and lactation, when the fetal and infant DHA requirement is 100–200 mg/day (Clandinin et al., 1980a,b; Haggarty, 2004). A female child must store this DHA at the same time that she requires substantial amounts of DHA to support her own growth and development. Because she must allocate some of her limited dietary $n-3$ to storing DHA for her future children, there is a competition between her need for DHA for her own body and brain and her need to store DHA for future reproduction. Girls with proportionally larger amounts of gluteofemoral fat and lower waist-hip ratios have earlier menarche (Lassek and Gaulin, 2007). While human males usually have much less adipose than females, they have substantially more than typical primates (Pond and Mattacks, 1987).

The optimal amount of DHA per day in children has not been established, but participants in a 1999 workshop sponsored by National Institutes of Health recommended that at least 0.1% of calories should be DHA (Simopoulos and Leaf, 1999), which would be 220 mg for a 2000 calorie (8.4 MJ) diet (assuming 9 calories/g of fat). Similar amounts are recommended for pregnant and nursing women (Koletzko et al., 2007.) The per capita amount of DHA and ALA in the American food supply in 1990 was 70 mg and 2.4 g respectively (Gerrior et al., 2004).

While $n-3$ fatty acids are known to have positive effects on cognition, less is known about the effects of $n-6$ fatty acids, such as linoleic (LA, 18:2n−6) and arachidonic acid (AA, 20:4n−6). As with $n-3$, some form of $n-6$ must come from the diet, and there is no interconversion of $n-3$ and $n-6$ fatty acids. In the terrestrial synthetic pathway that evolved to elongate ALA, the LA-to-arachidonic conversion competes for the same enzymes used to synthesize DHA from ALA (Rubin and Laposata, 1992; Emken et al., 1994; Innis et al., 2004; Hibbeln et al., 2006; Harnack et al., 2009; Gibson et al., 2011). Because of this metabolic competition, higher $n-6$ fatty acid intake might be expected to have negative effects on cognition; and four studies have shown this (Agostoni et al., 1997; Whalley et al., 2004; Novak et al., 2008; Neggers et al., 2009).

Amounts of $n-3$ fatty acids have declined in the American diet during the twentieth century while $n-6$ have increased (Blasbalg et al., 2011). Reconstructions of the paleolithic diet suggest that over most of human evolution, there was more $n-3$ than $n-6$ in the diet (Kuipers et al., 2010). Per capita linoleic acid in the American food supply was 29.3 g in 1990 and the ratio of total $n-6$ to $n-3$ was 12.3 (Gerrior et al., 2004). Because of their metabolic competition for necessary enzymes, the very high amount of $n-6$ linoleic acid compared with $n-3$ in the diet of American children is likely to decrease the conversion rate of ALA to DHA.

Larger, population-based samples may help to clarify the relationships between fatty acid consumption and cognitive performance. Cognitive and dietary data collected in the Third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988–1994 provides an opportunity to examine the relationship between dietary $n-3$ and $n-6$ fatty acid intake and cognitive outcomes in a large sample of American children, as well as the possible effects of other nutrients. We recently found a relationship between lower maternal waist–hip ratios and cognitive performance which may be mediated by $n-3$ fatty acids (Lassek and Gaulin, 2008). This leads us to predict that dietary $n-3$ will also be positively related to cognitive outcomes in this sample, whereas dietary $n-6$ will be inversely related to the same outcome measures. Because of the much greater requirement for $n-3$ fatty acids in human females, we predict that their cognitive performance will be more sensitive to the amount of $n-3$ in the diet and to the competing effects of dietary $n-6$.

MATERIALS AND METHODS

Detailed dietary histories based on 24-h recall were obtained by skilled interviewers for 13,923 males and 15,182 females aged 0–90 in the NHANES III sample, 1988–1994. From this larger sample we restricted our focus to children 6–16 years old. The child sample included 26% non-Hispanic whites, 35% non-Hispanic blacks, 35% Mexican-Americans, and 5% other. Because of the oversampling of blacks and Hispanics, this sample is not representative of the American population.

Twenty-four hour dietary recall was used to estimate individual intake. Specific fatty acid content of the foods consumed was estimated using the food database of the University of Minnesota's Nutrition Coordinating Center, and for other nutrients, the USDA National Nutrient Database for Standard Reference (USDA). Nutrients used in the analysis which were estimated by conjoining the dietary histories and food composition databases in this way included vitamins A, B_6, B_{12}, C, and E, iron, folate, riboflavin, niacin, and thiamine, serum electrolytes, specific sugars, saturated fats with 10, 12, 14, 17, 18, 20, and 22 carbons, monounsaturated fats with 14, 16, 18, 20, and 22 carbons, the $n-6$ fatty acids LA and AA (summed for total $n-6$), the $n-3$ fatty acids ALA, EPA, DPA, and DHA (added together for total $n-3$), and total saturated, monounsaturated, and polyunsaturated fats.

Four cognitive tests were administered to 2253 males and 2309 females aged 6–16 in the NHANES III sample, including the math and reading tests from the Wide Range Achievement Test-Revised and the digit span and block design tests from the Wechsler Intelligence Scale for Children-Revised. The mean scaled score across these four tests was used as a measure of cognitive performance for each of the 6–16 year-olds in this study; both cognitive scores and dietary data were available for 2103 females and 2051 males, and these subgroups thus comprise our primary sample.

Other (non-dietary) measures included in the analyses as possible confounding variables include race/ethnicity, family income, family size, and years of education of the householder parent. Serum lead was also included because it is known to have a significant negative relationship with cognitive performance in

children (Wasserman et al., 1997; Needleman and Landrigan, 2004). Multiple linear regression was performed using SPSS-17. Sample weights and complex adjustments for the sampling methodology were not used; this is in accordance with the recommendations of Korn and Graubard (1991).

RESULTS

Table 1 provides descriptive statistics for the children in the study sample. Mean energy intake was 20% higher in males and dietary fatty acid intakes showed similar differences; the mean test score and ratio of $n-6$ to $n-3$ was higher in females. Dietary intakes of fatty acids show a high degree of individual variation.

Based on stepwise multiple regression, **Table 2** shows the effect of significant nutrients on the cognitive performance of the children in the sample, controlling for race/ethnicity, family income

Table 1 | Mean and SD by sex (data from NHANES III, ages 6–16).

Variable	Male	SD	Female	SD	Ratio m/f
N	2103		2051		
Age	10.5	3.1	10.7	3.1	0.98*
Parent education, years	10.8	3.8	10.8	3.9	1.01
Family size	5.1	1.9	5.1	1.8	1.01
Summed test scores	7.7	2.7	7.9	2.6	0.97*
Daily energy intake (MJ)	9.4	4.2	7.8	3.1	1.21***
Serum lead, (mg)	3.7	3.3	2.8	2.6	1.31***
LA, (g)	13.5	10.2	11.9	9.3	1.14***
AA, (g)	0.13	0.15	0.10	0.14	1.25***
Total $n-6$, (g)	13.6	10.3	12.0	9.3	1.14***
ALA, (g)	1.3	0.9	1.1	0.8	1.16***
EPA, (g)	0.018	0.014	0.092	0.092	1.26***
DPA, (g)	0.008	0.004	0.037	0.023	1.74***
DHA, (g)	0.044	0.173	0.032	0.115	1.39**
Total $n-3$, (g)	1.4	1.0	1.2	0.8	1.17***
Ratio of $n-6/n-3$	10.6	6.9	11.1	8.7	0.96*

*$p < 0.05$ **$p < 0.001$ ***$p < 0.00001$ for differences in means.*

Table 2 | Standardized regression coefficients for the effect of dietary fatty acids on performance on four cognitive tests in youth 6–16, NHANES III.

	Females	Males
N	2103	2051
Age	−0.103***	−0.052*
Race/ethnicity	0.175***	0.209***
Family income	0.206***	0.165***
Parental education	0.192***	0.145***
Family size	−0.068*	−0.055*
Serum lead	−0.080***	−0.153***
Dietary $n-3$	0.098**	0.049*
Dietary $n-6$	−0.062*	
r^2	0.242***	0.227***

*$p < 0.05$ **$p < 0.001$ ***$p < 0.00001$.*

and size, years of education of the householder parent, and serum lead. For both sexes, total dietary $n-3$ fatty acids are significantly positively related to test scores, while for females, total $n-6$ fatty acids are negatively related. None of the other 33 nutrients are significantly related, including iron and folate and total dietary saturated, monounsaturated, and polyunsaturated fatty acids. Based on its unstandardized regression coefficient, an increase in daily $n-3$ intake of 1 g increases the average test score by 0.38 points (±0.09 SD) in females and by 0.19 points (±0.10 SD) in males; this represents 0.14 and 0.07 of the SDs for the test scores. In females, but not males, when the ratio of $n-6$ to $n-3$ was used in place of the separate $n-3$ and $n-6$ intakes in the regression, it was significantly and negatively related to the cognitive score (beta = −0.071, $p = 0.001$). When the regression was run with both sexes, sex was not a significant variable.

National Health and Nutrition Examination Survey may sample more than one member in participating households; this creates a lack of independence among cases that is potentially problematic. To examine whether this lack of independence may have favored our hypothesis, we repeated the analysis using both sexes of children and limiting the sample to one child per household (1581 boys; 1682 girls), and found that there was no difference in the results of the regression.

DISCUSSION

Using a large sample drawn from NHANES III, dietary $n-3$ fatty acids are positively related to cognitive performance in children 6–16 years of age, while $n-6$ fatty acids are negatively related to cognitive performance in females in the same sample. As predicted, the contribution of dietary $n-3$ to cognitive performance is much greater (two-fold) in females, and females also show a significant negative effect for $n-6$ fatty acids which compete with $n-3$ for enzymes needed in the biosynthesis of DHA.

This result controls for other relevant variables known to affect cognitive outcomes. The special effects of $n-3$ and $n-6$ are apparent because dietary consumption of 33 other fatty acids and nutrients are not related to cognitive outcome measures based on the same dietary data set and the same children. The positive cognitive effect of dietary $n-3$ fatty acids, as measured by the imperfect method of 24-h recall, is of greater magnitude in girls than the negative effect of serum lead, a well known influence on cognition in children. Dietary iron and folate, which have also been found to relate to cognitive performance in some studies of children (Arija et al., 2006), were not significant when added to this regression.

Because of the complex sampling method used in the NHANES, these results should be viewed with caution and should not be considered representative of the American population. Also, the diet estimates used in this study were based on a single 24-h recall; and while this type of assessment is related to the long-term diet, it is not a highly accurate measure (Knutsen et al., 2003; Sekula et al., 2005; Slater et al., 2010). In addition, the children in the sample are past the ages of maximal brain growth, a period when the effects of dietary fatty acids would be expected to be greater. However, despite these limitations, their cognitive ability is still related to the amount of dietary $n-3$ fatty acids, and of the 40 nutritional

variables used in the analysis, only $n-3$ and $n-6$ fatty acids were significantly related to cognitive ability.

The stronger effect of $n-3$ and significantly negative effect of $n-6$ in girls may reflect their greater need for $n-3$ fatty acids to sustain future pregnancy and lactation, as explained above. Because stored maternal fat is selectively used to support the development of the fetal and infant brain – via the placenta and breast milk – females must prepare for these demands by storing DHA in fat at a much higher rate than males during their childhood and adolescence, while their own brains and bodies are still growing. This competition between growth and reproductive goals, absent in boys, may make girls more subject to the antagonism between the $n-6$ and $n-3$ fatty acid families in commandeering necessary synthetic enzymes.

The effect of dietary fatty acids on cognition demonstrated here is relatively small – but of similar magnitude to the negative effect of lead. Both are environmental variables that can be altered, and clear steps have been taken in the case of lead. Since more than half of the variance in cognition is heritable (Plomin et al., 2000), and other environmental variables are often intractable (e.g., family income), dietary fatty acid intake may be of significant pragmatic importance.

These findings on the relationship between dietary fatty acids and cognitive performance are of particular interest in relation to current American food consumption patterns. The cognitive effects of dietary fatty acids in American children may be greater than in other populations because of the limited amount of $n-3$ fatty acids in the American diet combined with unusually high levels of $n-6$ (Blasbalg et al., 2011). Based on the energy intake of the sample children, the recommended amount of 0.1% of energy

for DHA would be 250 in males and 210 mg in females per day. Assuming a very generous conversion rate of 2% for ALA to DHA, the mean total daily amount of DHA for the sample children would be just 70 mg for males and 54 mg for females, considerably short of the recommended amounts.

A coordinated increase in $n-6$ and decrease in $n-3$ supplies are the hallmarks of modern American industrial food production, and reflected in the high $n-6/n-3$ ratios in the NHANES III sample. Corn, which increased by 78% in the US diet from 1970 to 2000 (Putnam et al., 2002), has an $n-6/n-3$ ratio of 34 to 1 (USDA). Soybean oil, especially when partially hydrogenated or made from prevalent low-ALA varieties of soybeans, has a similarly high ratio. Moreover, $n-3$ in processed food is often removed because it is prone to spoil and thus reduces product shelf life (Holman, 1998).

An experimental study in rats using feeds corresponding to the Japanese diet (high $n-3$, low $n-6$) and American diet (high $n-6$, low $n-3$) found both better learning and many more synapses in the hippocampus in the rats fed the "Japanese" diet (Yoshida et al., 1997). It thus seems possible that the high $n-6/n-3$ ratio in the American diet might contribute to the relatively low ranking of American children in international testing (NCES, 2005) compared to children in countries with lower $n-6/n-3$ ratios, like Japan. Thus, evolutionary considerations may help lead to findings with considerable potential public health significance.

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