Distribution Agreement

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my Thesis in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this Thesis. I retain all ownership rights to the copyright of the Thesis. I also retain the right to use in future works (such as articles or books) all or part of this Thesis.

_____ _____

Diana Diaz Date

Serum Acrylamide Level and Self-Reported Health Status in U.S. Women of Reproductive Age, NHANES 2003-2004

BY

Diana Diaz
Degree to be Awarded: M.P.H
Executive MPH

_____

Vijaya Kancherla, Ph.D. Date

_____

Hind Beydoun, Ph.D. Date

_____

Melissa Alperin, MPH, MCHES Date
Chair, Executive MPH program

Serum Acrylamide Level and Self-Reported Health Status in U.S. Women of Reproductive Age, NHANES 2003-2004

BY

Diana Diaz
M.P.H., Emory University, 2015
B.S., University of North Georgia, 2009

Thesis Committee Chair: Vijaya Kancherla, Ph.D.

An abstract of
a Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master in Public Health
in the Executive MPH Program
2015

Abstract

Serum Acrylamide Level and Self-Reported Health Status in U.S. Women of Reproductive Age, NHANES 2003-2004

BY
Diana Diaz

BACKGROUND: Acrylamide is a chemical compound formed in foods processed at high temperatures (frying and baking). Dietary exposure to acrylamide has been associated with adverse birth outcome in humans; however, evidence has been inconclusive and requires further investigation.
METHODS: Using data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES), we conducted a cross-sectional study to examine the association between serum acrylamide levels and self-reported health among women of reproductive age. Using multivariable logistic regression, we estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs). We also examined interaction between acrylamide and race and ethnicity, age, serum cotinine level, and frequency of restaurant foods consumption per week.
RESULTS: The mean serum acrylamide level among women who reported poor health status was 93.05 pmol/G Hb compared to 78.81pmol/G Hb in those with good health status (P value = 0.01). Multivariable logistic regression showed a positive, but non-significant association between highest quartile of serum acrylamide exposure and poor self-reported health (aOR=1.82; 95% CI= 0.91, 3.70), controlling for age, race and ethnicity, education, citizenship status, family income, number of times health care was utilized in the previous years, and serum cotinine levels. There was significant effect modification due to the race (p=0.03) and serum cotinine (p=0.001) on the association between serum acrylamide levels and self-reported health among study participants.
CONCLUSIONS: High serum acrylamide level was associated with the self-reported health status among women of reproductive age in the NHANES, and the effect is further modified by race and ethnicity. Future studies should examine the association in a prospective study design.

Serum Acrylamide Level and Self-Reported Health Status in U.S. Women of Reproductive Age, NHANES 2003-2004

BY

Diana Diaz
M.P.H, Emory University, 2015
B.S., North Georgia College and State University, 2009

Thesis Committee Chair: Vijaya Kancherla, Ph.D.

A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Executive MPH program
2015

ACKNOWLEDGEMENTS

I would like to sincerely thank Vijaya Kancherla, Ph.D. and Hind Beydoun, Ph.D for their unwavering guidance and patience throughout the writing of this thesis. Additionally, I would like to thank Emory University for allowing me an educational opportunity that I would not have otherwise had the ability to pursue, through their Employee Courtesy Scholarship program. My studies at Emory University have opened doors for me I never would have imagined. Special thanks are in order for the Executive Master's in Public Health administration, for their flexibility in scheduling around my life events, which has allowed me to complete this thesis and apply for graduation at the end of Summer 2015.

A special thanks is owed to my family. Their understanding and patience over the last two years while I have been learning the skills that allowed me to culminate my studies with the following thesis has been a cornerstone in this towering achievement. And finally, thanks to God and the living Christ, the foundation of my efforts to help promote health for the indigent and disenfranchised in rural America, for allowing me to live to see this come to pass, for lending me the strength to endure.

Table of Contents

Serum Acrylamide Level and Self-Reported Health Status in U.S. Women of Reproductive age, NHANES2003-2004

Diana Diaz, MPH(c)

Vijaya Kancherla, Ph.D.,
Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA

Hind Beydoun, Ph.D.
Graduate Program in Public Health, Eastern Virginia Medical School, Norfolk, VA

Corresponding author: TBD

Short Title: Acrylamide and Self-Reported Health in WOCBP

The authors declare no competing financial interests.

ABSTRACT

BACKGROUND: Acrylamide is a chemical compound formed in foods processed at high temperatures (frying and baking). Dietary exposure to acrylamide has been associated with adverse birth outcome in humans; however, evidence has been inconclusive and requires further investigation.
METHODS: Using data from the 2003-2004 National Health and Nutrition Examination Survey (NHANES), we conducted a cross-sectional study to examine the association between serum acrylamide levels and self-reported health among women of reproductive age. Using multivariable logistic regression, we estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs). We also examined interaction between acrylamide and race and ethnicity, age, serum cotinine level, and frequency of restaurant foods consumption per week.
RESULTS: The mean serum acrylamide level among women who reported poor health status was 93.05 pmol/G Hb compared to 78.81pmol/G Hb in those with good health status (P value = 0.01). Multivariable logistic regression showed a positive, but non-significant association between highest quartile of serum acrylamide exposure and poor self-reported health (aOR=1.82; 95% CI= 0.91, 3.70), controlling for age, race and ethnicity, education, citizenship status, family income, number of times health care was utilized in the previous years, and serum cotinine levels. There was significant effect modification due to the race (p=0.03) and serum cotinine (p=0.001) on the association between serum acrylamide levels and self-reported health among study participants.
CONCLUSIONS: High serum acrylamide level was associated with the self-reported health status among women of reproductive age in the NHANES, and the effect is further modified by race and ethnicity. Future studies should examine the association in a prospective study design.

EXPANDED INTRODUCTION

Acrylamide is an industrial chemical that has received recent attention as a neurotoxin and potential teratogen (U.S. Dept. of Health and Human Services, 1992). Acrylamide is ubiquitous as a precursor to copolymers and polymers and is generally used as a precipitating agent in water and waste treatments, pulp and paper industry, oil production, and is found in adhesives, dyes, grouting material, and as a stabilizer in soils (Dearfield, 1988; Manson, 2005). While the main non-occupational exposure to acrylamide occurs through smoking, non-industrial applications of acrylamide constitute significant potential human exposures outside occupation and smoking. Non-occupational uses of acrylamide include its addition in soaps and cosmetics as a thickening agent, as well as to products for hair, skin, and even products used for denture placement (Dearfield, 1988; Manière, 2005). More recently, it has been found that significant levels of acrylamide are generated in foods that are fried and baked at high temperatures (Tareke, 2002).

Acrylamide has been well-researched in relation to cancer. Studies in rodents have shown that acrylamide administration in rats caused increases in tumors after relatively low, chronic doses of dietary exposure (Damjanov, 1998). In male rats such cancers included tunica vaginalis mesotheliomas and carcinoma of the thyroid gland; while in females they showed mammary gland fibroadenomas and adenocarcinomas, follicular adenomas, and carcinomas of the thyroid (Damjanov, 1998; Johnson, 1986).

In addition to its tumorigenic effects, acrylamide has been shown to be a reproductive toxicant in rodents, causing extensive post-implantation loss in female rats at high doses (Zenick, 1986). Acrylamide is classified as a clastogen, a compound that can enhance breakage of DNA strands and disruption of chromosomes causing dominant lethality in progeny (Rutledge, 1990;

Shelby, 1986; Smith, 1986; Tyla, 2000). It has also been shown to negatively impact sperm quality and quantity (Adler, 1994; Gutierrez-Espeleta, 1992; Pruser, 2011; Smith, 1986; Titenko-Holland, 1998; Tyl, 2003). Studies in both animal models and humans associate acrylamide with developmental abnormalities (Titenko-Holland, 1998; Holland, 1999; Marchetti, 2009) and adverse birth outcomes, such as low birth weight, altered organogenesis, and increased infant mortality (El-Sayyad, 2011; El-Sayyad, 2011; Wise, 1995).

Animal (rat, mouse, guinea pig, and Musca domestica) models demonstrate that acrylamide has significant reproductive toxicity that affects both parents and resulting progeny (Dearfield, 1995; Hulas-Stasiak, 2013; Zenick, 1986) and that these effects have been shown to intensify across generations in mice (Chapin, 1995). In rats, acrylamide exposure has been associated with reduced vaginal patency, reduced rates of pregnancy, changes in copulatory behaviors, decreased maternal weight, decreased maternal weight gain during pregnancy, and reduced numbers of progeny with reduced birth weights occurring at each mating (El-Sayyad, 2011; Friedman, 1999; Wise, 1995; Zenick, 1986). Many of these results were obtained from animal exposure to prolonged, low-doses of dietary acrylamide before mating and during pregnancy and/or lactation, and the negative reproductive effects of acrylamide were often more pronounced than its neurotoxic effects (Chapin, 1995).

Researchers hypothesize that oxidative stress is the mechanism for some of the negative effects that acrylamide has on developing offspring and reproducing adults (Allam, 2010; Allam, 2011). The clastogenic action of acrylamide on sperm quality and quantity were mainly thought to be responsible for decreased size of litters and reduced birth weight of pups, until further research implicated maternal exposures to acrylamide in the development of fetal abnormalities (Tyl, 2003) which are thought to be a product of the oxidative stress that acrylamide induces

both in maternal tissues as well as in the developing neonate. As acrylamide has been shown to cross the placenta in both animals and humans (Annola, 2008; Schettgen, 2004; Sörgel, 2002), it is also important to understand its role in human reproduction. Few studies have been conducted assessing the reproductive effects of acrylamide on humans.

After the discovery that significant levels of acrylamide are generated in foods that are fried and baked at high temperatures, an evaluation of common foods was conducted to determine their respective average levels of acrylamide (Tareke, 2002). The highest concentrations of acrylamide were found in carbohydrate rich foods prepared at high temperatures. An estimated average daily intake of 100 micrograms was estimated for a sample of the Swedish population, and was defined as a non-negligible cancer risk (Tareke et al. 2002). Utilizing data on average acrylamide intakes across five different countries (the United States, Australia, Sweden, the Netherlands, and Norway) and average daily adult consumption averaged between 0.3 to 0.8 µg/kg per day, with children having up to three times that rate (Manson et al. 2005). The MoBa study including over 50,500 women in Norway, examined self-reported food intake during pregnancy and birth weights and gestational age among offspring. Dietary acrylamide intake was associated with reduced fetal growth; children born to mothers in the highest quartile of acrylamide intake weighed almost 26 grams less than those children born to mothers in the lowest quartile of acrylamide intake (Duarte-Salles, 2013). The NewGeneris study found that maternal hemoglobin adducts of acrylamide were associated with statistically significant reductions in both birth weight and head circumference, and that this effect was similar in non-smokers versus smokers (Pedersen, 2012). This significant finding demonstrates that exposures from dietary acrylamide can mirror the effects of more traditional sources of exposures to acrylamide such as smoking and occupational exposures. Both studies present

information on the effects of serum acrylamide on neonates, but do not specifically address the effect of acrylamide and adducts on maternal health. It is known that pre-pregnancy and pre-natal health are important to ensuring the reduction of adverse birth outcomes. There is ample evidence to indicate that maintenance of proper nutrition is necessary in order to foster an ideal internal environment for future conception (Abu-Saad, 2010). Additionally, self-reported fair or poor health both before and after delivery is associated with increased likelihood of delivery of a low birth weight or preterm baby (Teoli, 2015).

To address the lack of studies conducted in the United States on the topic of acrylamide and its effects on the overall health of women of reproductive age, we examined the association between serum acrylamide levels and its effects on self-reported health status among non-pregnant women of reproductive age (15-44 years) in the 2003-2004 National Health and Nutrition Examination Survey (NHANES). The 2003-2004 period was chosen because it is the latest cycle where both serum acrylamide levels and self-reported health status were measured by NHANES, proving a unique opportunity to conduct our analysis. It is well known that pre-pregnancy health is associated with pregnancy outcomes and healthier children, and often supplants even the most thorough prenatal care given to women in reducing premature birth, especially in the poor and minorities (Dillard, 2004). We hypothesize that serum acrylamide is associated with the health status (self-reported) in non-pregnant women of reproductive age (15-44 years) participating in NHANES (2003-2004).

INTRODUCTION FOR PUBLICATION

Acrylamide is a reproductive toxicant chemical used as a precipitating agent in water and waste treatments, pulp and paper industry, and oil production that is also found in adhesives, dyes, grouting material, and as a stabilizer in soils, as well as in cosmetics, lotions, and denture adhesives (Dearfield, 1988; Manière, 2005; Manson, 2005). In the early 2000s, acrylamide was recognized to be generated in foods that are fried and baked at high temperatures , with the highest concentrations of acrylamide occurring in carbohydrate rich foods prepared at high temperatures, with potatoes, potato chips, and crisp (non-soft) breads identified as having the highest amount of acrylamide among foods studied (Tareke, 2002). Utilizing data on average acrylamide intakes across five different countries (the United States, Australia, Sweden, the Netherlands, and Norway) an average daily adult consumption averaged between 0.3 to 0.8 µg/kg per day, with children having up to three times that rate (Manson, 2005).

Concerns for the effects of acrylamide on maternal and child health are numerous. Studies confirm the presence of acrylamide in cord blood, its ability to cross the placenta and its presence in fetal circulation (Annola, 2008; Schettgen, 2004; von Stedingk, 2011). Both experimental and observational studies in animals and humans demonstrate that acrylamide has significant reproductive toxicity that affects both parents and resulting progeny (Dearfield, 1995; Hulas-Stasiak, 2013; Zenick, 1986), and that these effects appear to intensify across generations (Chapin, 1995). The contributions of maternal effects due to acrylamide exposure on outcome in progeny cannot be ignored, as effects seen in offspring where both parents are exposed cannot solely be explained by known clastogenic effects on sperm (Tyl and Friedman 2003). Common observations from animal models on the impact of acrylamide on maternal outcomes included reduced vaginal patency, reduced rates of pregnancy, changes in copulatory behaviors, decreased

maternal weight, decreased maternal weight gain during pregnancy, and reduced numbers of progeny with reduced birth weights occurring at each mating. (El-Sayyad, 2011b; Friedman, 1999; Wise, 1995; Zenick, 1986). Many of these results were obtained from animal exposures to prolonged, low-dose exposures before mating and during pregnancy and lactation, and the negative reproductive effects of acrylamide were often more pronounced than its neurotoxic effects (Chapin, 1995).

Our recent systematic review of literature reveals that there are no studies in the United States that investigate the relationship between acrylamide exposure and maternal and child health (Diaz et al., 2015 – unpublished findings). Two studies conducted in Europe address the effects of maternal acrylamide exposure and the outcomes of children born to them (Duarte-Salles, 2013; Pedersen, 2012). The MoBa study which included over 50,500 mothers in Norway, linked data collected on self-reported food intake during pregnancy and data on birth weights and gestational age for their children and found that oral acrylamide intake was associated with reductions fetal growth. In this study, children born to mothers in the highest quartile of acrylamide intake weighted almost 26 grams less than those children born mothers in the lowest quartile of acrylamide intake (Duarte-Salles, 2013). The NewGeneris study found that maternal hemoglobin adducts of acrylamide were associated with statistically significant reductions in both birth weight and head circumference, and that this effect was similar in non-smokers versus smokers (Pedersen et al. 2012). This significant finding demonstrates that exposures from dietary acrylamide can mirror the effects of more traditional sources of exposures to acrylamide such as smoking and occupational exposures. Both studies present information on the effects of serum acrylamide on neonates, but do not specifically address the effect of acrylamide and adducts on

maternal health. It is known that pre-pregnancy and pre-natal health are important to ensuring the reduction of adverse birth outcomes.

There is ample evidence to indicate that maintenance of proper nutrition is necessary in order to foster an ideal internal environment for future conception (Abu-Saad, 2010). Excellent pre-pregnancy health is associated with better pregnancy outcomes and healthier children, and often supplants even the most thorough prenatal care given to women in reducing premature birth, especially in the poor and in minorities (Dillard 2004). Additionally, self-reported fair or poor health both before and after delivery is associated with increased likelihood of delivery of a low birth weight or preterm baby (Teoli, 2015).

To address the lack of studies conducted in the United States on the topic of acrylamide and its effects on the overall health of women of reproductive age, we examined the association between serum acrylamide levels and its effects on self-reported health status among non-pregnant women of reproductive age (15-44 years) in the 2003-2004 National Health and Nutrition Examination Survey (NHANES). The 2003-2004 period was chosen because it is the latest cycle where both serum acrylamide levels and self-reported health status were measured by NHANES, proving a unique opportunity to conduct our analysis. It is well known that pre-pregnancy health is associated with pregnancy outcomes and healthier children, and often supplants even the most thorough prenatal care given to women in reducing premature birth, especially in the poor and minorities (Dillard, 2004). We hypothesize that serum acrylamide is associated with the health status (self-reported) in non-pregnant women of reproductive age (15-44 years) participating in NHANES (2003-2004). In conducting this analysis, we hope to add to the current body of epidemiologic literature on the effects of acrylamide on the health of women

in the United States, and help generate new hypotheses for future analyses in this important but sparsely explored area of human health.

METHODS

NHANES is an ongoing, nationally representative, cross-sectional survey series of about 5000 persons in the United States each year, with a changing focus on a variety of health and nutrition measurements to meet emerging needs of the population. It was initiated in the early 1960s as a program of studies to assess the health and nutritional status of adults and children in the United States. Specifically, NHANES is designed based on a four-stage stratified cluster sample of counties, census blocks, domestic units and household members selected from the 50 United States. NHANES participants are representative of non-institutionalized civilian population of the 50 United States and District of Columbia (Zipf, 2013). NHANES uniquely combines interviews and physical examinations conducted among its participants. The interview includes demographic, socioeconomic, dietary, and health-related questions. The physical examination part includes medical, dental, and physiological measurements, as well as laboratory tests administered by highly trained medical personnel. NHANES is overseen by the National Center for Health Statistics (NCHS), at the Centers for Disease Control and Prevention (CDC). The study was approved by the institutional review board of National Center for Health Statistics, and a written informed consent was obtained by the NCHS from all study participants (Zipf, 2013). Institutional Review Board at Emory University provided an exemption of review for the current study.

Study Population

Our study population is comprised of reproductive aged, non-pregnant women (15-44 years) participating in 2003-2004 NHANES (henceforth referred to as 'women aged 15-44 years'), and those that had provided blood samples for serum acrylamide levels for medical examinations conducted for NHANES. The 2003-2004 cycle was chosen as this was the latest

cycle that could avail measures of self-reported health in the interview data and link it to the serum acrylamide measurements collected as a part of laboratory analysis. We also excluded individuals with missing information on acrylamide (n=511) and those with missing information on self-reported health (n=1). We further excluded women with missing information on current pregnancy or those with a confirmed pregnancy (n=227; 15.3%). Women who were excluded from our analysis due to missing serum acrylamide values differed significantly from women that had these values in the following: age, race and ethnicity, health status, level of education, citizenship status, annual family income, country of birth, and in number of times health care services were utilized in the past year (Table 4). Thus, our final analysis was based on 2711 non-pregnant women aged 15-44 years.

Outcome Variable

The outcome of our study was self-reported health among women aged 15-44 years in the 2003-2004 NHANES. We dichotomized self-reported health outcomes based on the responses women provided for the survey question: "Would you say your general health is: 1. Excellent; 2. Very Good 3. Good 4. Fair 5. Poor?". For our analysis, we pooled responses indicating 'excellent', 'very good', or 'good health' into a new category 'Good Self-Reported Health' and responses indicating 'fair' or 'poor' into another new category 'Poor Self-Reported Health'.

Exposure Variable

NHANES 2003-2004 cycle measured hemoglobin adducts of acrylamide in human whole blood samples were measured for all women included in the analysis. Acrylamide was analyzed using a modified Edman reaction to test for the reaction products of the N-terminal valine of hemoglobin proteins with acrylamide, resulting in measurements of picomoles of adduct per gram of hemoglobin (pmoL/G Hb). The samples were sent to the Division of Environmental

Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for storage and analysis. Hemoglobin adducts of serum acrylamide to red blood cells (erythrocytes) act as a biomarker for acrylamide exposure over approximately 120 days (the life of an erythrocyte) (Annola et al. 2008; Duarte-Salles et al. 2013; Pedersen et al. 2012; Schettgen et al. 2004; von Stedingk et al. 2011).

Covariables

The following covariables were examined for confounding and interaction: participant's age in years (15-20, 21-34, 35-44), race and ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Other), health status compared to previous year (better, worse, about the same), marital status (married, unmarried), level of education attained (less than high school, high school diploma/GED, more than high school), citizenship status (U.S. citizen, non-citizen), annual family income (U.S. $) (<35,000, ≥35,000), country of birth (born in 50 United States or Washington D.C., born in Mexico, born elsewhere), number of times health care was utilized in the last year (0, 1-9, 10 or more times), household size (continuous), frequency of restaurant food consumption per week (continuous), and serum cotinine levels in ng/mL (as an indicator for smoking status) (continuous). Serum cotinine levels were dichotomized as 'current smokers' (≥200 ng/mL) and 'not current smokers' (<200 ng/mL) based off of clinical cut points for serum cotinine in smokers versus non-smokers used by the Mayo Clinic. (http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82509).

Statistical Analysis

Accounting for the complex survey sampling design of NHANES throughout our analysis, we conducted descriptive analysis to compare both categorical and continuous variables for demographic and health characteristics comparing women with good and poor self-reported

health. We examined the association between self-reported health and acrylamide exposure by comparing each quartile of acrylamide level to the lowest quartile (<25th percentile) and estimating crude and adjusted odds ratios (cORs and aORs, respectively) and 95% confidence intervals (CIs). Quartiles were derived by using values of serum acrylamide (pmoL/G Hb) among women who reported good health (Quartile 1=0-<43.6, Quartile 2=43.6-<57.6, Quartile 3=57.6-<87.1, Quartile 4=≥87.1). All covariables were selected based on *a priori* criterion depending on previous literature. A covariable was retained for inclusion in the multivariable models if the exposure estimate changed by 15% when the covariable was deleted from the model. We used unconditional logistic regression to determine the association between acrylamide levels and the self- reported health outcomes in women aged 15-44 years. Models were built based on backward selection procedures. Race and ethnicity, age, serum cotinine level, and number of times restaurant foods are consumed per week were assessed for interaction. If an interaction term was significant (p value < 0.05) in a multivariable model, we reported aORs and 95% CI from the final model including significant interaction terms, and from stratum-specific analysis for each of the significant variable that modified the effect between serum acrylamide and self-reported health status. All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA.)

RESULTS

Of the 2711 women eligible for our analysis, 2361 (88.21%) were classified as having good self-reported health and 350 (11.79%) were classified as having poor self-reported health. The mean serum acrylamide level among women who reported poor health status was 93.05 pmol/G Hb compared to 78.81pmol/G Hb in those with good health status (P value = 0.01). When we compared serum acrylamide levels (quartiles) between the two study groups, the majority of women with self-reported poor health (38.44%) were grouped in the highest quartile of serum acrylamide level (≥87.1 pmol/ G Hb) (Table 1).

Overall, women with poor self-reported health differed from their counterparts in several demographic and health characteristics (Table 1). For example, women with poor self-reported health were significantly more likely to be in the upper age range among women of reproductive age (35-44 years), and non-Hispanic black or Hispanic, compared to women reporting good health. Women with poor self-reported health had significantly higher odds of reporting that their health status was worse during the NHANES survey year compared to the previous year. The two study groups also differed significantly based on their the level of education attained, i.e., about 54% of women reporting health had more than high school education compared to only 25% in the groups with poor self-reported health. They also had an annual family income less than $35,000 compared to their counterparts (P value = <0.001). Majority of women reporting poor health status were non-citizens (22.8% vs. 10.9%; P value = <0.001). Women reporting poor health status were significantly more likely to be born outside the Unites States. Women in both groups averaged approximately four members per household, while women reporting poor health consumed restaurant foods approximately 2.70 times per week versus those with good health, who consumed these foods 3.35 times per week (P value = 0.003). Women with poor

self-reported health averaged 71.05 ng/mL of serum cotinine levels and 93.05 pmol/G Hb of serum acrylamide (P value = 0.001) (Table 1).

In the unadjusted analysis, lower level of serum acrylamide exposure (Quartile 2 vs. Quartile 1) provided a significant protective effect for poor health (cOR=0.57, 95% CI=0.37, 0.87). The higher quartile of exposure (≥87.1 pmoL/G Hb) had a positive but non-significant association with poor health outcome (cOR=1.42, 95% CI=0.87, 2.28) (Table 1). In the multivariable model, the protective effect noted in the Quartile 2 persisted, but became statistically non-significant (aOR=0.68, 95% CI=0.40, 1.16) after controlling for age, race and ethnicity, education, citizenship, annual family income, number of times health care was utilized in the past year, serum cotinine, and the effect modification terms for acrylamide and race, and acrylamide and cotinine. Further, although statistically insignificant, the positive risk association between serum acrylamide level and poor health noted in the unadjusted analysis further increased in the multivariable analysis after controlling for the aforementioned covariables (aOR=1.83, 95% CI=0.91, 3.70), indicating a potential risk of poor health among women represented in the Quartile 4 compared to women in the Quartile 1 (Table 2).

As mentioned above, there was a significant interaction between serum acrylamide level and race and ethnicity, and serum acrylamide and serum cotinine levels in our analysis. Results from our multivariable stratum-specific analysis show that the magnitude of association between serum acrylamide level and poor health varied between different race and ethnic groups. The risk of reporting poor health status was highest among Hispanic women represented in the highest quartile of acrylamide exposure compared to Hispanic women in the lowest quartile (aOR=1.70, 95% CI=0.55, 5.26). A similar positive, but insignificant association was noted among non-

Hispanic White women in the Quartile 4 compared to their counterparts in the Quartile 1 (aOR=1.47, 95% CI=0.78, 2.77) (Table 3).

Multivariable stratum-specific analysis based on cigarette smoking status showed that women who smoked had a significantly lower risk of self-reported poor health if they were in the lower quartile of serum acrylamide exposure (quartile 2 vs. quartile 1) after adjusting for potential confounders (aOR=0.12, 95% CI=0.04, 0.36) (Table 4). The risk of poor health status was not associated with any of the higher quartiles of serum acrylamide exposures for both smokers and non-smokers. The interaction between acrylamide and smoking warrants further investigation in future studies.

DISCUSSION

This analysis provides a novel insight into the association between serum acrylamide level and self-reported health status among a population-based sample of non-pregnant reproductive aged women in the NHANES 2003-2004 survey. We found that women in the lower quartiles of serum acrylamide levels had a significant protective effect on self-reported poor health; and women in the higher quartile of acrylamide exposure had a borderline positive, but non-significant association with poor self-reported health. The outcomes differed by race and ethnicity, and the participants' smoking status. As no previous studies have been conducted examining the effect of serum acrylamide on self-reported health or other markers of general health in women and children, we were unable to compare our findings with past studies. We believe that our analysis is hypothesis generating for future studies given present day chronic exposure to acrylamide in foods and environment.

The impact of race and ethnicity and smoking on the main hypothesis needs replication and further study. Whether there is a genetic mechanism that explains the variability of effect sizes in our noted association between serum acrylamide and health status is worth exploring. The significant interaction noted between acrylamide and cotinine level is another interesting findings which needs further study. Non-smoking women had similar non-significant reduced odds of reporting poor health across all quartiles when compared to non-smoking women in the lowest quartile, with these odds being about 30% less than the odds of reporting poor health in each of the quartiles versus those in the first quartile. In a different and unrelated hypothesis, the NewGeneris study found that smoking was not an effect modifier in an association between maternal acrylamide level and birth weight and head circumference in the offspring (Pedersen et

al. 2012). The association between cotinine, acrylamide and health status of reproductive aged women needs further study.

There are several strengths in our study. This work provides information in a novel area that has not previously been explored in looking in the effects of serum acrylamide on the self-reported health of women of reproductive age. The study was based on a population-based dataset and is a benchmark national health survey in the United States. The survey employs validated examination measures, concomitant biological specimen collection, with collection of measures of health status, and high quality of data collection enhanced by high response rate along with national representativeness (Institute of Medicine Committee on a National Surveillance system for Cardiovascular and Select Chronic Diseases, 2011). This is also the first study where we had laboratory measurement of serum acrylamide and self-reported health status in a nationally representative dataset. Studies have confirmed that standardized, self-reported health status measures, such as those collected in the NHANES interview questionnaire, are a valid measure of health in epidemiologic research and that this is generalizable to many different societal conditions (Miilunpalo, 1997).

Our study is not without limitations. The dichotomization of the health outcomes might have decreased the sensitivity of the analysis in such a way that masks significant associations between more granular measures of self-reported health, that is, the grouping of five health rankings into two dichotomous categories might have hidden a significant association between serum acrylamide levels and health outcomes. However, the current design mitigates small numbers in grouping when more granular categories of self-reported health are used. We also had to exclude some women due to missing data; our analysis compared the groups of women who were excluded based on missing information to the group that was included in the final

analysis and revealed significant differences between the groups (Appendix 1). Potential reasons for the differences found between the two groups may rest in the study criteria of our analysis, which could show significant differences in variables such as age and race when comparing the very large group of included women versus those that were excluded. For example, the differences found between the groups in terms of race can may be attributable to chance as a result of multiple comparisons, or be a symptom of differential participation in NHANES by a certain race. This may also be the case for women who do not have citizenship or were not born in the United States, as a language barrier or illegal status may have caused differing participation rates versus the women in the included group. Our analyses rely on a self-reported health outcome and are therefore subject to recall bias as well as a measure of social desirability bias. In addition to these potentially significant weaknesses, the cross sectional nature of the data does not allow a direct association to be ascertained between serum acrylamide and health outcome, as there is no way to tell if health outcomes are impacting serum acrylamide levels or if serum acrylamide levels are impacting self-reported health outcomes in this study. Considering that 99% of participants in NHANES had measurable levels of acrylamide in their sera, and as randomized clinical trials would be unethical considering the designation of acrylamide as a potential human carcinogen, the conduct of prospective longitudinal studies is the best tool in understanding the effects of serum acrylamide on health outcomes in this vulnerable population.

About 50% of all births in the US are unplanned, and as a result diets of women of reproductive age may not be optimal for conception and prenatal health of the fetus at least during the periconceptional period (one month before and three months after conception). Knowledge regarding the effects of acrylamide on the health status of women of child bearing potential in the United States may provide an important target in the reduction of adverse birth

outcomes including teratogenicity, prematurity, and low birth weight babies in the United States. This will indeed help in reducing the burden to life and economy that is associated with these outcomes. For some minorities, the potential of losing even one ounce of birth weight can mean the difference between life and death, as seen in African American infants, who are more than twice as likely as white counterparts to die during the first year of life due to low birth weight (Collins, 2004).

In conclusion, our study is prompts further investigation into the role of acrylamide exposure on the health of women. Future studies may use a prospective cohort study design to further understand the association. As the majority of participants in our study had detectable levels of acrylamide in their blood, it is important to know the full scope of the implications of this finding given the knowledge that acrylamide is a known teratogen and neurotoxicant. Serum acrylamide surveillance efforts should continue so that accurate information on the persistence and decrease or increase of acrylamide levels in humans can be ascertained.

EXPANDED DISCUSSION

This analysis provides a novel insight into the association between serum acrylamide level and self-reported health status among a population-based sample of non-pregnant reproductive aged women in the NHANES 2003-2004 survey. We found that women in the

lower quartiles of serum acrylamide levels had a significant protective effect on self-reported poor health; and women in the higher quartile of acrylamide exposure had a borderline positive, but non-significant association with poor self-reported health. The outcomes differed by race and ethnicity, and the participants' smoking status. As no previous studies have been conducted examining the effect of serum acrylamide on self-reported health or other markers of general health in women and children, we were unable to compare our findings with past studies. We believe that our analysis is hypothesis generating for future studies given present day chronic exposure to acrylamide in foods and environment.

The impact of race and ethnicity and smoking on the main hypothesis needs replication and further study. The effects of race on the relationship between serum acrylamide and self-reported health are intriguing. Hispanic and white women had high, non-significant positive odds ratios when compared to women in the first quartiles. Interestingly, black women and women of other race had odds ratios in for women in the highest quartile that showed a protective effect of serum acrylamide. Understanding all the determinants of maternal health may help to reduce the disparities in birth outcomes that can be seen in the United States, which includes investigation into biochemical differences between the races that convey greater risk or lessened risk for poor health outcomes. As previously mentioned, the negative effects of acrylamide are thought to be related to its ability to cause oxidative stress. Our findings prompt investigations into whether there is a genetic mechanism that explains the variability of effect sizes in our noted association between serum acrylamide and health status, including whether there are racial differences in the effects or occurrence of oxidative stress in response to acrylamide exposure.

The significant interaction noted between acrylamide and cotinine level is another interesting finding which needs further study. Non-smoking women had similar non-significant

reduced odds of reporting poor health across all quartiles when compared to non-smoking women in the lowest quartile, with these odds being about 30% less than the odds of reporting poor health in each of the quartiles versus those in the first quartile. In a different and unrelated hypothesis, the NewGeneris study found that smoking was not an effect modifier in an association between maternal acrylamide level and birth weight and head circumference in the offspring (Pedersen et al. 2012). The association between cotinine, acrylamide and health status of reproductive aged women needs further study.

There are several strengths in our study. This work provides information in a novel area that has not previously been explored in looking in the effects of serum acrylamide on the self-reported health of women of reproductive age. The study was based on a population-based dataset and is a benchmark national health survey in the United States. The survey employs validated examination measures, concomitant biological specimen collection, with collection of measures of health status, and high quality of data collection enhanced by high response rate along with national representativeness (Institute of Medicine Committee on a National Surveillance system for Cardiovascular and Select Chronic Diseases, 2011). This is also the first study where we had laboratory measurement of serum acrylamide and self-reported health status in a nationally representative dataset. Studies have confirmed that standardized, self-reported health status measures, such as those collected in the NHANES interview questionnaire, are a valid measure of health in epidemiologic research and that this is generalizable to many different societal conditions (Miilunpalo, 1997).

Our study is not without limitations. The dichotomization of the health outcomes might have decreased the sensitivity of the analysis in such a way that masks significant associations between more granular measures of self-reported health, that is, the grouping of five health

rankings into two dichotomous categories might have hidden a significant association between serum acrylamide levels and health outcomes. However, the current design mitigates small numbers in grouping when more granular categories of self-reported health are used. We also had to exclude some women due to missing data; our analysis compared the groups of women who were excluded based on missing information to the group that was included in the final analysis and revealed significant differences between the groups (Appendix 1). Potential reasons for the differences found between the two groups may rest in the study criteria of our analysis, which could show significant differences in variables such as age and race when comparing the very large group of included women versus those that were excluded. For example, the differences found between the groups in terms of race can may be attributable to chance as a result of multiple comparisons, or be a symptom of differential participation in NHANES by a certain race. This may also be the case for women who do not have citizenship or were not born in the United States, as a language barrier or illegal status may have caused differing participation rates versus the women in the included group. Our analyses rely on a self-reported health outcome and are therefore subject to recall bias as well as a measure of social desirability bias. In addition to these potentially significant weaknesses, the cross sectional nature of the data does not allow a direct association to be ascertained between serum acrylamide and health outcome, as there is no way to tell if health outcomes are impacting serum acrylamide levels or if serum acrylamide levels are impacting self-reported health outcomes in this study. Considering that 99% of participants in NHANES had measurable levels of acrylamide in their sera, and as randomized clinical trials would be unethical considering the designation of acrylamide as a potential human carcinogen, the conduct of prospective longitudinal studies is the best tool in understanding the effects of serum acrylamide on health outcomes in this vulnerable population.

About 50% of all births in the US are unplanned, and as a result diets of women of reproductive age may not be optimal for conception and prenatal health of the fetus, at least during the periconceptional period (one month before and three months after conception). Knowledge regarding the effects of acrylamide on the health status of women of child bearing potential in the United States may provide an important target in the reduction of adverse birth outcomes including teratogenicity, prematurity, and low birth weight babies in the United States. This will indeed help in reducing the burden to life and economy that is associated with these outcomes. For some minorities, the potential of losing even one ounce of birth weight can mean the difference between life and death, as seen in African American infants, who are more than twice as likely as white counterparts to die during the first year of life due to low birth weight (Collins, 2004).

Knowledge regarding the effects of acrylamide on the health status of women of child bearing potential in the United States may provide an important target in the reduction of prematurity and low birth weight children born in the United States, reducing the burden to life and economy that is associated with these outcomes. To gain this knowledge, further studies will generate understanding of the full implications of dietary acrylamide on the health of reproductive-aged women and may then translate into recommendations that positively affect maternal health and the health of the fetus, neonate, and postnatal infant. Although our study did not find significant confounding or interaction with the number of times women consumed restaurant foods weekly, home diets rich in acrylamide that are consumed more regularly may be more directly relevant to serum acrylamide values. Though this study cannot directly implicate diet as contributing to the findings of positive association between serum acrylamide and self-reported health, previous findings in the literature have shown that dietary acrylamide can cause

adverse health effects and birth outcomes in animals and humans, as discussed previously. Thus, a suggested recommendation for women of reproductive age to avoid frequent consumption of acrylamide rich foods during their reproductive years is merited based on the findings.

Although the findings in our study were not statistically significant, the positive association and gains in the confidence interval seen in the odds ratios for women with the highest level of serum acrylamide versus those with the lowest, may represent an effect that has some clinical import. Based on these results, a clear need for further investigation into this association and its implications on the health of women of reproductive age is merited. Further investigations may elucidate trends that are clinically important, and ideally, will lead to studies that are prospective in nature comparing women of reproductive age with high consumption of acrylamide rich foods to those with diets characterized by low consumption of acrylamide rich foods. The findings of this paper impress a need to discover the intricacies of the relationship between health and serum acrylamide levels, in light of what is known about this chemical as a reproductive and neurological toxicant, in addition to what has been revealed in regards to the effects on neonatal outcomes in seen in recent human epidemiologic studies. Given the great many questions that remain, the work done here generates a recommendation to resume serum acrylamide monitoring as a protocol for the NHANES study, as only one cycle of NHANES collected data for serum acrylamide between 2003 and 2004.

In conclusion, our study is prompts further investigation into the role of acrylamide exposure on the health of women. Future studies may use a prospective cohort study design to further understand the association. As the majority of participants in our study had detectable levels of acrylamide in their blood, it is important to know the full scope of the implications of this finding given the knowledge that acrylamide is a known teratogen and neurotoxicant. Serum

acrylamide surveillance efforts should continue so that accurate information on the persistence and decrease or increase of acrylamide levels in humans can be ascertained.

Table 1. Characteristics of U.S. women of reproductive age (15-44 years) by self-reported health status, National Health and Nutrition Examination Survey, 2003-2004.

Characteristics of WOCBP	Good Self-Reported Health **(N=2361)** *Frequency (Weighted %)*	Poor Self-Reported Health **(N=350)** *Frequency (Weighted %)*	Unadjusted Odds Ratios OR (95% CI)	P value
Serum Acrylamide[a]				
Quartile 1 (0 - < 43.6 pmoL/G Hb)	552 (24.76)	95 (26.65)	1.00	<.0003
Quartile 2 (43.6 - < 57.6 pmoL/G Hb)	621 (22.2)	68 (15.42)	**0.57 (0.37, 0.87)**	
Quartile 3 (57.6 - <87.1 pmoL/G Hb)	631 (24.99)	87 (19.49)	0.72 (0.51, 1.02)	
Quartile 4 (≥87.1 pmoL/G Hb)	557 (25.03)	108 (38.44)	1.42 (0.87, 2.28)	
Age[b]				
15-20 years	1098 (19.92)	109 (11.79)	1.00	0.002
21-34 years	743 (44.50)	116 (41.37)	1.57 (0.97,2.54)	
35-44 years	520 (35.57)	125 (46.84)	**2.23 (1.45, 3.43)**	
Race and Ethnicity[b]				
White, Non-Hispanic	963 (68.97)	102 (52.33)	1.00	<.0003
Black, Non-Hispanic	681 (11.97)	89(16.00)	**1.75 (1.21, 2.56)**	
Hispanic	635 (14.23)	144 (26.12)	**2.35 (1.49, 3.70)**	
Other Race	82 (4.44)	35 (5.55)	1.64 (0.79, 3.41)	
Health Status Compared to One Year Ago[a]				
Better	578 (19.98)	64 (17.83)	1.00	<.007
Worse	164 (7.03)	78 (21.60)	**3.31 (1.71, 6.42)**	
About the same	1813 (72.99)	240 (60.57)	0.94 (0.56,1.58)	
Marital Status[b]				
Married	778 (43.60)	118 (39.44)	1.00	0.35
Not Married	1777 (56.41)	264 (60.56)	0.86 (0.60,1.22)	
Level of Education[b]				
Less Than High School	1022 (22.72)	200(45.76)	1.00	<.0001
High School Diploma/GED	480(23.30)	77 (29.02)	**0.61 (0.38,0.98)**	
More Than High School	858 (53.98)	72 (25.22)	**0.23 (0.15,0.36)**	
Citizenship Status[b]				
U.S. Citizen	2035 (89.09)	249 (77.16)	1.00	<.0001
Non-Citizen	326 (10.91)	101 (22.84)	**2.47 (1.54, 3.77)**	
Annual Family Income (U.S. Dollars)[b]				
<34,999	1180 (40.29)	248 (66.64)	1.00	<.0001
≥$35,000	1149 (59.71)	98 (33.36)	**2.94 (2.20, 3.93)**	
Country of Birth[b]				
United States	1911 (83.92)	236 (72.96)	1.00	0.003
Mexico	247 (5.66)	80 (13.40)	**2.73 (1.81, 4.10)**	
Other	203 (10.42)	34 (13.63)	1.50 (0.80, 2.84)	
# of Times Health Care Utilized in Past Year[a]				
None	459 (19.24)	72 (20.03)	1.00	0.001
1-9 times	1713 (71.85)	220 (59.39)	1.26 (0.76, 2.08)	
10 or more times	186 (8.90)	58 (20.59)	**2.80 (1.69, 4.62)**	
Household Size[b]	***Mean*** ± SD	***Mean*** ± SD		
# of Times/Week Restaurant Foods Consumed[b]	3.95 (1.63)	4.01 (1.70)	1.06 (0.93,1.20)	0.38
Serum Cotinine Level (ng/mL)	3.35 (3.35)	2.70 (2.74)	0.89 (0.82, 0.97)	0.003
Serum Acrylamide Level (*pmoL/G Hb*)	50.09 (109.7)	71.05 (121.4)	1.002 (1.001,1.003)	0.01
	78.81	93.05	1.004 (1.001,1.006)	0.01

[a] Sum of weights for MEC data= 360983376. [b] Sum of weights for interview data = 359,633,508

Table 2. Multivariable analysis to examine the between serum acrylamide level and self-reported health status among US women of reproductive age (14-55 years) participating in the National Health and Nutrition Examination Survey (NHANES) 2003-2004.

Characteristics	Adjusted OR (95% CI)[a]
Serum acrylamide	
Quartile 1 (0 - <43.6 pmoL/G Hb)	1.00
Quartile 2 (43.6 - < 57.6 pmoL/G Hb)	0.68 (0.40, 1.16)
Quartile 3 (57.6 - <87.1 pmoL/G Hb)	0.999 (0.65, 1.53)
Quartile 4 (≥87.1 pmoL/G Hb)	1.83 (0.91, 3.70)
Age[c]	
15-20 years	1.00
21-34 years	**2.35 (1.16, 4.77)**
35-44 years	**3.90 (2.04, 7.47)**
Race and Ethnicity[c]	
White, Non-Hispanic	1.00
Black, Non-Hispanic	**1.63 (1.09, 2.43)**
Hispanic	**2.78 (1.57, 4.92)**
Other Race	1.57 (0.79, 3.12)
Education[c]	
Less than high school	1.00
High school diploma/GED	**0.50 (0.27, 0.93)**
More than high school	**0.23 (0.12, 0.43)**
Citizenship[c]	
US citizen	1.00
Non-US Citizen	1.77 (0.88, 3.58)
Annual family income (US dollars) [c]	
<34,999	1.00
≥35,000	**0.47 (0.33, 0.68)**
# times health care utilized in the past year[c]	
None	1.00
1-9 times	1.28 (0.70, 2.34)
10 or more times	**3.71 (1.89, 7.27)**
Serum Cotinine (ng/mL) [b]	1.005 (0.0998, 1.012)
Acrylamide[b] * Race[c]	**0.95 (0.910, 0.993)**
Acrylamide[b] * Serum Cotinine[c]	0.999 (0.997, 1.001)

[a]Each variable is adjusted for all other variables in the table
OR=Odds Ratio; CI=Confidence Interval
[b]Sum of weights for MEC data=360,983,376; [c]Sum of weights for interview data=359,633,508

Table 3. Association between serum acrylamide level and self-reported health status in reproductive age women (15-44 years) in relation to race and ethnicity - National Health and Nutrition Examination Survey (NHANES) 2003-2004

	Adjusted OR (95% CI Intervals)			
	White Non-Hispanic	**Black Non-Hispanic**	**Hispanic**	**Other**
Serum Acrylamide (pmoL/G Hb) [a]				
Quartile 1 (0-< 43.6)	1.00	1.00	1.00	1.00
Quartile 2 (43.6-< 57.6)	0.64 (0.29, 1.39)	0.53 (0.18, 1.56)	0.57 (0.26, 1.22)	0.11 (0.01, 2.30)
Quartile 3 (57.6-<87.1)	1.03 (0.52, 2.05)	0.52 (0.16, 1.64)	0.77 (0.41, 1.45)	<0.001(<0.001, <0.001)
Quartile 4 (≥87.1)	1.47 (0.78, 2.77)	0.38 (0.12, 1.25)	1.70 (0.55, 5.26)	<0.001(<0.001, 1.03)

[a]Adjusted for age, education, citizenship status, number of times healthcare services accessed in the past year, average annual household income, in the presence of interaction between serum acrylamide and serum cotinine levels.

Table 4. Association between serum acrylamide level and self-reported health status in reproductive age women in relation to serum cotinine levels - National Health and Nutrition Examination Survey (NHANES), 2003-2004

	Adjusted OR (95% CI Intervals)	
	Serum Cotinine: Non-Smoker (<200.0ng/mL)[b]	**Serum Cotinine: Smoker (>200.0ng/mL)[b]**
Serum Acrylamide (pmoL/G Hb)[a]		
Quartile 1 (0-< 43.6)	1.00	1.00
Quartile 2 (43.6-< 57.6)	0.74 (0.39, 1.39)	0.12 (0.04, 0.36)
Quartile 3 (57.6-<87.1)	1.00 (0.60, 1.68)	0.17 (0.01, 2.10)
Quartile 4 (≥87.1)	1.69 (0.65, 4.37)	0.13 (0.01, 1.85)

[a]Adjusted for age, education, citizenship status, number of times healthcare services accessed in previous 1 year, average annual household income, in the presence of interaction between serum acrylamide and race/ethnicity.

[b]Serum cotinine dichotomized based off of clinical cut points for serum cotinine in smokers versus non-smokers used by the Mayo Clinic. (http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/82509).

References

Abu-Saad K, Fraser D. 2010. Maternal nutrition and birth outcomes. Epidemiol Rev 32:5-25.

Adler ID, Reitmeir P, Schmoller R, Schriever-Schwemmer G. 1994. Dose response for heritable translocations induced by acrylamide in spermatids of mice. Mutat Res 309:285-291.

Allam A, El-Ghareeb AA, Abdul-Hamid M, Baikry A, Sabri MI. 2011. Prenatal and perinatal acrylamide disrupts the development of cerebellum in rat: Biochemical and morphological studies. Toxicol Ind Health 27:291-306.

Allam AA, El-Ghareeb AW, Abdul-Hamid M, Bakery AE, Gad M, Sabri M. 2010. Effect of prenatal and perinatal acrylamide on the biochemical and morphological changes in liver of developing albino rat. Arch Toxicol 84:129-141.

Annola K, Karttunen V, Keski-Rahkonen P, Myllynen P, Segerbäck D, Heinonen S, et al. 2008. Transplacental transfer of acrylamide and glycidamide are comparable to that of antipyrine in perfused human placenta. Toxicol Lett 182:50-56.

Chapin R, Fail P, George J, Grizzle T. 1995. The reproductive and neural toxicities of acrylamide and three analogues in swiss mice, evaluated using the continuous breeding protocol. Toxicol Sci 27:9-24.

Collins JW, David RJ, Handler A, Wall S, Andes S. 2004. Very low birthweight in african american infants: The role of maternal exposure to interpersonal racial discrimination. Am J Public Health 94:2132-2138.

Crimmins EM, Saito Y. 2001. Trends in healthy life expectancy in the united states, 1970-1990: Gender, racial, and educational differences. Soc Sci Med 52:1629-1641.

Damjanov I, Friedman MA. 1998. Mesotheliomas of tunica vaginalis testis of fischer 344 (f344) rats treated with acrylamide: A light and electron microscopy study. In Vivo 12:495-502.

Dearfield KL, Abernathy CO, Ottley MS, Brantner JH, Hayes PF. 1988. Acrylamide: Its metabolism, developmental and reproductive effects, genotoxicity, and carcinogenicity. Mutation Research/Reviews in Genetic Toxicology 195:45-77.

Dearfield KL, Abernathy CO, Ottley MS, Brantner JH, Hayes PF. 1988. Acrylamide: Its metabolism, developmental and reproductive effects, genotoxicity, and carcinogenicity. Mutat Res 195:45-77.

Dearfield KL, Douglas GR, Ehling UH, Moore MM, Sega GA, Brusick DJ. 1995. Acrylamide: A review of its genotoxicity and an assessment of heritable genetic risk. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis 330:71-99.

Dillard R. 2004. Improving pre-pregnancy health is key to reducing infant mortality. N C Med J 65:147-148.

Duarte-Salles T, von Stedingk H, Granum B, Gutzkow KB, Rydberg P, Tornqvist M, et al. 2013. Dietary acrylamide intake during pregnancy and fetal growth-results from the norwegian mother and child cohort study (moba). Environ Health Perspect 121:374-379.

El-Sayyad HI, Abou-Egla MH, El-Sayyad FI, El-Ghawet HA, Gaur RL, Fernando A, et al. 2011a. Effects of fried potato chip supplementation on mouse pregnancy and fetal development. Nutrition 27:343-350.

El-Sayyad HI, El-Gammal HL, Habak LA, Abdel-Galil HM, Fernando A, Gaur RL, et al. 2011b. Structural and ultrastructural evidence of neurotoxic effects of fried potato chips on rat postnatal development. Nutrition 27:1066-1075.

El-Sayyad HI, Sakr SA, Badawy GM, Afify HS. 2011c. Hazardous effects of fried potato chips on the development of retina in albino rats. Asian Pacific journal of tropical biomedicine 1:253-260.

Friedman MA, Tyl RW, Marr MC, Myers CB, Gerling FS, Ross WP. 1999. Effects of lactational administration of acrylamide on rat dams and offspring. Reprod Toxicol 13:511-520.

Gutierrez-Espeleta GA, Hughes LA, Piegorsch WW, Shelby MD, Generoso WM. 1992. Acrylamide: Dermal exposure produces genetic damage in male mouse germ cells. Fundam Appl Toxicol 18:189-192.

Holland N, Ahlborn T, Turteltaub K, Markee C, Moore D, 2nd, Wyrobek AJ, et al. 1999. Acrylamide causes preimplantation abnormalities in embryos and induces chromatin-adducts in male germ cells of mice. Reprod Toxicol 13:167-178.

Hulas-Stasiak M, Dobrowolski P, Tomaszewska E, Kostro K. 2013. Maternal acrylamide treatment reduces ovarian follicle number in newborn guinea pig offspring. Reprod Toxicol 42:125-131.

Institute of Medicine (US) Committee on a National Surveillance System for Cardiovascular and Select Chronic Diseases. 2011. A Nationwide Framework for Surveillance of Cardiovascular and Chronic Lung Diseases. Washington (DC): National Academies Press.

Johnson KA, Gorzinski SJ, Bodner KM, Campbell RA, Wolf CH, Friedman MA, et al. 1986. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of fischer 344 rats. Toxicol Appl Pharmacol 85:154-168.

Kancherla V, Romitti PA, Sun L, Carey JC, Burns TL, Siega-Riz AM, et al. 2014. Descriptive and risk factor analysis for choanal atresia: The national birth defects prevention study, 1997-2007. Eur J Med Genet 57:220-229.

Ku L, Waidmann. T. 2003 How race/ethnicity, immigration status and language affect health insurance coverage, access to care and quality of care among the low-income population. Publication #4132. Available at http://www.kff.org.

Ma Y, Shi J, Zheng M, Liu J, Tian S, He X, et al. 2011. Toxicological effects of acrylamide on the reproductive system of weaning male rats. Toxicol Ind Health 27:617-627.

Manière I, Godard T, Doerge DR, Churchwell MI, Guffroy M, Laurentie M, et al. 2005. DNA damage and DNA adduct formation in rat tissues following oral administration of acrylamide. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 580:119-129.

Manson J, Brabec MJ, Buelke-Sam J, Carlson GP, Chapin RE, Favor JB, et al. 2005. Ntp-cerhr expert panel report on the reproductive and developmental toxicity of acrylamide. Birth Defects Res B Dev Reprod Toxicol 74:17-113.

Marchetti F, Bishop J, Lowe X, Wyrobek AJ. 2009. Chromosomal mosaicism in mouse two-cell embryos after paternal exposure to acrylamide. Toxicol Sci 107:194-205.

Pedersen M, von Stedingk H, Botsivali M, Agramunt S, Alexander J, Brunborg G, et al. 2012. Birth weight, head circumference, and prenatal exposure to acrylamide from maternal diet: The european prospective mother-child study (newgeneris). Environ Health Perspect 120:1739-1745.

Pruser KN, Flynn NE. 2011. Acrylamide in health and disease. Frontiers in bioscience (Scholar edition) 3:41-51.

Rutledge JC, Cain KT, Kyle J, Cornett CV, Cacheiro NL, Witt K, et al. 1990. Increased incidence of developmental anomalies among descendants of carriers of methylenebisacrylamide-induced balanced reciprocal translocations. Mutat Res 229:161-172.

Schettgen T, Kutting B, Hornig M, Beckmann MW, Weiss T, Drexler H, et al. 2004. Trans-placental exposure of neonates to acrylamide--a pilot study. Int Arch Occup Environ Health 77:213-216.

Shelby MD, Cain KT, Hughes LA, Braden PW, Generoso WM. 1986. Dominant lethal effects of acrylamide in male mice. Mutat Res 173:35-40.

Smith MK, Zenick H, Preston RJ, George EL, Long RE. 1986. Dominant lethal effects of subchronic acrylamide administration in the male long-evans rat. Mutat Res 173:273-277.

Sörgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A, et al. 2002. Acrylamide: Increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans. Chemotherapy 48:267-274.

Tareke E, Rydberg P, Karlsson P, Eriksson S, Törnqvist M. 2002. Analysis of acrylamide, a carcinogen formed in heated foodstuffs. J Agric Food Chem 50:4998-5006.

Teoli DA, Zullig KJ, Hendryx MS. 2015. Maternal fair/poor self-rated health and adverse infant birth outcomes. Health Care Women Int 36:108-120.

Titenko-Holland N, Ahlborn T, Lowe X, Shang N, Smith MT, Wyrobek AJ. 1998. Micronuclei and developmental abnormalities in 4-day mouse embryos after paternal treatment with acrylamide. Environ Mol Mutagen 31:206-217.

Tyl RW, Friedman MA. 2003. Effects of acrylamide on rodent reproductive performance. Reprod Toxicol 17:1-13.

Tyla RW, Friedman MA, Losco PE, Fisher LC, Johnson KA, Strother DE, et al. 2000. Rat two-generation reproduction and dominant lethal study of acrylamide in drinking water. Reprod Toxicol 14:385-401.

U.S. Dept. of Health and Human Services PHS, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Standards Development and Technology Transfer, U.S. Department of Labor, Occupational Safety and Health Administration. 1992. Occupational safety and health guideline for acrylamide.

Williams DR. 1999. Race, socioeconomic status, and health the added effects of racism and discrimination. Ann N Y Acad Sci 896:173-188.

Wise LD, Gordon LR, Soper KA, Duchai DM, Morrissey RE. 1995. Developmental neurotoxicity evaluation of acrylamide in sprague-dawley rats. Neurotoxicol Teratol 17:189-198.

Zenick H, Hope E, Smith MK. 1986. Reproductive toxicity associated with acrylamide treatment in male and female rats. J Toxicol Environ Health 17:457-472.

Zipf G, Chiappa M, Porter KS, Ostchega Y, Lewis BG, Dostal J. 2013. National health and nutrition examination survey: Plan and operations, 1999-2010. Vital Health Stat 1:1-37.

Appendix Table 1. Comparison of characteristics of U.S. women of reproductive age that were included and excluded from the current analysis, National Health and Nutrition Examination Survey (NHANES), 2003-2004.

Characteristics	P value
Age[b]	<0.0001
Race and Ethnicity[b]	<0.0001
Health Status Compared to One Year Ago[a]	<0.0001
Marital Status[b]	<0.0001
Level of Education[b]	0.004
Citizenship Status[b]	<0.0001
Annual Family Income[b]	0.37
Country of Birth [b]	<0.0001
# of Times Health Care Utilized in Past Year[a]	<0.0001
Household Size[b]	<0.0001

[a]Sum of weights for MEC data=360,983,376; [b]Sum of weights for interview data=359,633,508