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# Jacobs Journal of Obesity

Research Article

## Overweight, Obesity, Perfluorooctanic Acid Exposure and Cardiovascular Risk Factors in an Appalachian Pediatric Population with Diabetes

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*Received:* 12-17-2015

*Accepted:* 01-15-2016

*Published:* 02-24-2016



### Abstract

#### Background

Obesity and cardiovascular risk factors among children with diabetes predisposes them to greater cardiovascular risk in adulthood. Exposure to perfluorooctanoic acid (C8), a synthetic bio-accumulating chemical, may exacerbate this relationship.

#### Objective

To determine the prevalence of obesity and cardiovascular risk factors in an Appalachian pediatric population with diabetes exposed to C8.

#### Methods

We used data on 114 children/adolescents (age<20 years, mean 13.4 years; 56% male, 95% White) with diabetes from West Virginia and Ohio, exposed to C8 contaminated drinking water. The age adjusted mean of serum cardiovascular risk factor biomarkers and the percentage of individuals with cardiovascular risk factors above the 97.5$^{th}$ percentile, or below the 2.5$^{th}$ percentile for HDL cholesterol, were calculated and assessed for trend across Centers for Disease Control and Prevention (CDC) standard pediatric Body Mass Index (BMI) category (<85th, 85th-95th, and >95th percentiles).

#### Results

Thirty-two percent of the population were obese and an additional 17% were overweight. Serum C8 level was correlated with total cholesterol and LDLc among those with BMI >95$^{th}$ percentile. LDLc, VLDLc, WBC count, and C-reactive protein increased with BMI category while HDLc decreased. Significant U-shaped trends across BMI category were detected for triglycerides, HDLc, white blood cell count, and C-reactive protein above the 97.5$^{th}$ percentile.

*Cite this article:* *Dodd K, Murray P, Fischl A, Costacou T, and Conway C. Overweight, Obesity, Perfluorooctanoic Acid Exposure, and Cardiovascular Risk Factors in an Appalachian Pediatric Population with Diabets. JJ Obesity. 2016. 2(1): 025.*

## Conclusions

The U-shaped relationship between BMI and cardiovascular risk factors suggests the overweight category is protective for children and adolescents with diabetes. C8 was associated with cardiovascular risk factors among the obese.

**Keywords:** Diabetes; C8; Cardiovascular risk; BMI percentile

## Introduction

There is evidence that children and adolescents from rural populations display greater rates of obesity than their urban counterparts [1]. Childhood obesity has been linked with pediatric Type 2 diabetes; however in recent years, pediatric obesity in Type 1 diabetes is becoming increasingly apparent. Associated with both types of diabetes and obesity among children are elevated rates of traditional cardiovascular disease risk factors, such as dyslipidemia, atherosclerosis, hypertension, and metabolic syndrome [2,3]. These risk factors are retained from childhood to adulthood and are predictive of cardiovascular disease in adults [4], which is the leading cause of death in adults with diabetes. These cardiovascular risk factors emerge during childhood but are frequently not recognized until later. This delay in diagnosis and treatment poses public and individual health concerns for overweight and obese children with diabetes [2,3,5].

In addition to traditional risk factors, perfluorooctanoic acid exposure has been associated with increased risk factors for cardiovascular disease [6]. Perfluorooctanoic acid (PFOA), commonly referred to as C8, is a synthetic chemical used extensively for industrial purposes in the production of products such as Teflon. This ubiquitous, degradation-resistant, water-soluble, bioaccumulating environmental toxin has been found in human tissues worldwide [7]. Animal models and epidemiologic studies have indicated that this toxin appears to affect growth and development, leading to obesity [7], and also has effects on cholesterol, uric acid, liver enzymes, and thyroid disease [8-11]. Children may accumulate greater serum concentrations of C8 than adults [12]. We sought to determine the prevalence of obesity and other elevated cardiovascular risk factors, and their inter-relatedness, in an Appalachian pediatric population with diabetes who had been exposed to C8.

## Methods

The C8 Health Project is a community-based study to investigate the effects of exposure to C8 contaminated drinking water [13]. The C8 Health Project was created as a result of a settlement agreement from the case of Jack W. Leach*, et al. v. E.I. du Pont de Nemours & Company* after it was found that C8 had contaminated the drinking water of six water districts in the mid-Ohio Valley between 1950 and 2004. Data from the C8 Health Project (n=69,030) was obtained for use in the current study.

A post-hoc agreement between the settling parties of the class action lawsuit created a population-wide health survey of the individuals affected by the C8 contamination. The health survey collected a wide range of serum and anthropometric measures to assess the potential link between C8 and human disease. Brookmar Inc., Parkersburg, West Virginia administered the consent process and data collection. Affirmation was required of minor adolescent participants after an explanation of the purpose and procedures of the survey. Parents or guardians of dependents aged <18 years were required to answer the survey for minors. Participants aged ≥18 years or <18 years, and independent from their parents, took the survey on their own. The phlebotomy laboratory contracted for the C8 Health Project provided standard consent and release forms to participants or their guardians. Brookmar, Inc. administered a separate consent form to obtain medical records from healthcare providers. We obtained institutional review board approval at West Virginia University for access to the C8 Health Project de-identified data for the following study.

The enrollment and data collection methods for the C8 Health Project occurred in 2005 and 2006, and have been described in detail previously [13]. Briefly, anthropometric measurements were self- or guardian-reported through a health survey of the participants. Medical documentation was obtained from health care providers to confirm self-reported medical diagnoses. Blood samples were obtained and clinical laboratory tests conducted at an accredited national laboratory. Laboratory tests included a lipid panel for total cholesterol, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglycerides. Low density lipoprotein cholesterol (LDL) was calculated by the Friedewald equation when triglycerides were less than 400.

The C8 Health Project population contained 14,573 children and adolescents aged <20 years. Participants with missing data on BMI percentile (n=1,390), those with an outlying BMI percentile (n=165), and those without diabetes (n=12,904) were excluded from analysis. The resulting study population consisted of 114 children and adolescents with diabetes. Individuals with a diagnosis for diabetes validated through review of medical records were included in analysis. Due to small sample sizes and missing data, we were unable to identify which type of diabetes mellitus individuals had. Additionally, for this study, individuals with a fasting glucose ≥126 mg/dl or a non-fasting glucose ≥200 mg/dl were considered to have diabetes.

Perfluoroalkylacid compounds (PFAA), including C8 were analyzed at a single commercial laboratory after serum was separated from participant blood samples and shipped on dry ice to the laboratory [13]. The protein precipitation extraction method with reverse phase high-performance liquid chromatography/tandem mass spectrometry was utilized for PFAA assays. A triple quadropole mass spectrometer in pre-selected reaction monitoring mode, monitoring for the M/Z transitions

of 10 PFAA species with an internal $^{13}C$ PFAA standard corresponding to the target compound was utilized for detection of PFAA. The results from the assay were transferred to the Windows-based information system of the C8 Health Project.

All statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC, USA). A SAS program obtained from the Centers for Disease Control and Prevention (CDC) website for growth chart training was used to calculate age-and sex-standardized BMI percentiles, based on the CDC year 2000 standard pediatric population [14]. The percentiles were then stratified into categories of normal (<85$^{th}$ percentile), overweight (85$^{th}$–95$^{th}$ percentile), and obese (>95$^{th}$ percentile) [15-16]. Correlations between serum cardiovascular risk factor biomarkers and C8 serum levels were tested within each category of BMI percentile. The Spearman Rank Correlation Coefficient and associated p-value was calculated for the following risk factors: total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, white blood cell count, C-reactive protein, and serum creatinine against serum C8. It was determined a priori that any material correlations between a variable and C8 would warrant adjustment for C8 in further analysis. A material correlation was considered an r>0.30 with a significance level at p=0.05.

The age adjusted mean and standard error of the mean (SEM) of serum cardiovascular risk factor biomarkers, listed above, were calculated for each category of BMI by applying least squares means in a general linear model. A linear contrast was used to test for a significant trend among these cardiovascular risk factors across BMI categories. National Health and Nutrition Examination Survey (NHANES) 2005-2006 data were used to calculate the age-and sex-standardized categories for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, white blood cell count, C-reactive protein, and serum creatinine, and weighting procedures were used to address the complex sample design of NHANES. We categorized individuals' risk factors into those with levels above the 97.5$^{th}$ percentile, or for HDL cholesterol, below the 2.5$^{th}$ percentile, according to the NHANES 2005-2006 data. An orthogonal polynomial contrast in logistic regression was used to test for quadratic trend among the percentage of individuals with cardiovascular risk factors above the 97.5$^{th}$ percentile, or below the 2.5$^{th}$ percentile for HDL cholesterol, by BMI category. A significance level of p<0.05 was utilized for all analyses.

## Results

Of the 114 children and adolescents with diabetes, 95% were white, 56% were male, 17% (n=19) were overweight, and 32% (n=37) were obese. The mean age was 13.4 years (SEM=0.4, range: 1–19 years), and the mean age and gender adjusted BMI percentile was 74.3 (SEM=27.4). Mean duration of diabetes, based on age of diagnosis and current age, was 4.7 years (SEM=3.2). Approximately, 33% of the study population reported an average household income of $20,000 or less.

The Spearman Rank Correlation coefficient for correlations between serum C8 and cardiovascular risk factors are shown in Table 1. In the 114 subjects with diabetes, only LDL cholesterol was positively significantly correlated to serum C8 (r=0.25, p=0.01); however, this correlation was not material. When stratified by BMI category, no variables were correlated with serum C8 within the <85$^{th}$ percentile and 85$^{th}$-<95$^{th}$ percentile categories. However, among those with a standardized BMI >95$^{th}$ percentile, total cholesterol and LDL cholesterol were directly significantly correlated with C8 (r= 0.34, p=0.05 and r=0.42, p=0.01, respectively).

The age adjusted means and SEM of cardiovascular serum biomarkers stratified by BMI category are presented in Table 2. A significant linear increase across BMI category was observed for LDL cholesterol, VLDL cholesterol, white blood cell count, and C-reactive protein. A significant decreasing trend across BMI category was observed for HDL cholesterol. An apparent U-shaped trend was seen across BMI categories for serum C8 and a linear trend for total cholesterol; however, neither attained statistical significance (p=0.12 and p=0.06, respectively). Diabetes duration had a significant U-shaped, or quadratic, relationship (p=0.04) with BMI category. No trend was observed for serum creatinine.

The percent of individuals with cardiovascular risk markers greater than the age-and sex-standardized 97.5$^{th}$ percentile for children and adolescents are reported in Table 3. The age range for children with at least 1 cardiovascular risk factor was from 4 to 19 years, with a mean of 15.0 years (SEM=0.4). Approximately, 91% of the population had two or more elevated cardiovascular disease risk factors and 5% of the population had elevations in all 7 risk factors. These data stratified by BMI category are depicted in Figure 1. Significant trends across BMI category were detected for total cholesterol, triglycerides, LDL cholesterol, white blood cell count, and C-reactive protein. C-reactive protein above the 97.5$^{th}$ percentile was the most prevalent (71.1%) among the cardiovascular risk factors in the total population. The prevalence of HDL cholesterol below the 2.5$^{th}$ percentile was 58.8%, and of triglycerides above the 97.5$^{th}$ percentile was 52.6%. Apparent U-shaped trends were seen for total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, white blood cell count, C-reactive protein, and serum creatinine. Significant quadratic trends were detected for triglycerides, HDL cholesterol, white blood cell count, and C-reactive protein.

**Table 1.** Correlations of Cardiovascular Risk Factors with Perfluorooctanoic Acid (C8) Stratified by Body Mass Index (BMI) Percentile Category, Spearman Rank Correlation Coefficient.

| | | BMI Percentile | | |
|---|---|---|---|---|
| | Overall | <85th | 85th-<95th | ≥95th |
| | 114 | 58 (51%) | 19 (17%) | 37 (32%) |
| BMI Percentile | 0.018 | -0.056 | -0.26 | -0.31† |
| Total Cholesterol (mg/dL) | 0.11 | 0.0036 | 0.069 | 0.34* |
| LDL Cholesterol (mg/dL) | 0.25* | 0.17 | 0.11 | 0.42* |
| VLDL Cholesterol (mg/dL) | 0.09 | 0.13 | -0.13 | 0.053 |
| HDL Cholesterol (mg/dL) | -0.16† | -0.21 | -0.22 | 0.0012 |
| Triglycerides (mg/dL) | 0.086 | 0.11 | -0.13 | 0.073 |
| White Blood Cell Count (x10e3/uL) | -0.027 | -0.046 | -0.19 | -0.24 |
| C-reactive Protein (mg/L) | -0.025 | -0.094 | -0.16 | -0.00033 |
| Serum Creatinine (mg/dL) | -0.012 | -0.013 | 0.092 | -0.12 |

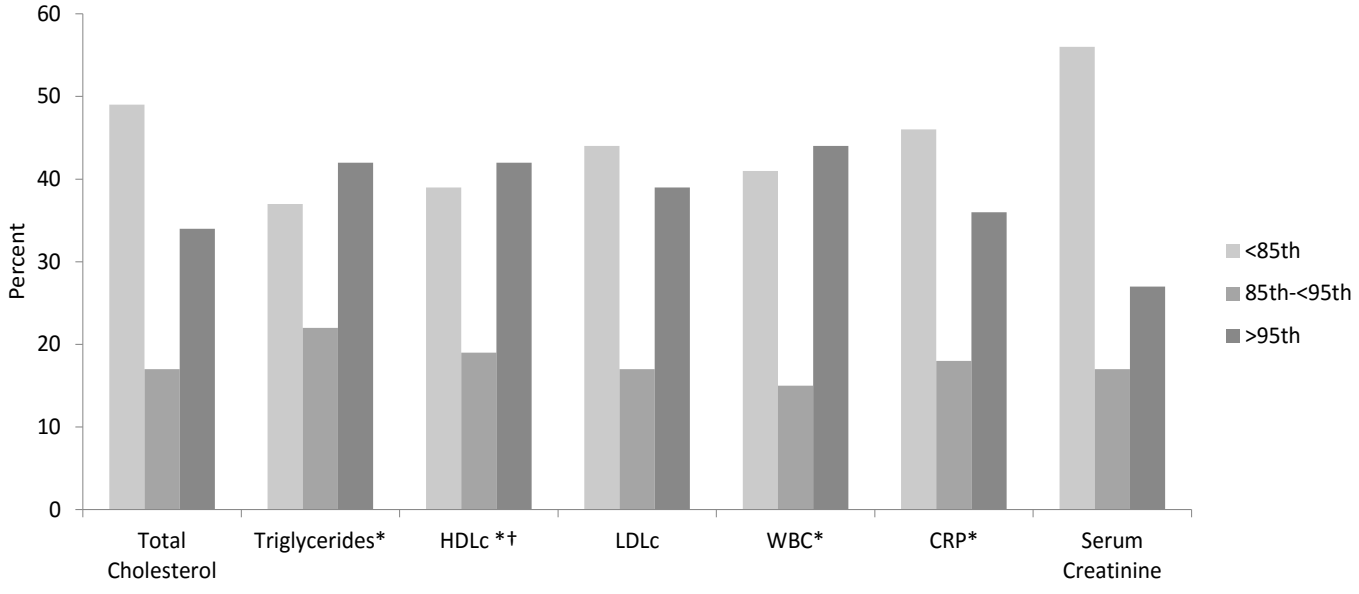
*p<0.05 †p<0.10

**Table 2.** Age Adjusted Cardiovascular and Metabolic Risk Factors by Body Mass Index (BMI) Category, mean (SEM).

| | BMI Percentile | | | p-trend* |
|---|---|---|---|---|
| | <85th | 85th-<95th | >95th | |
| N(%) | 58 (51%) | 19 (17%) | 37 (32%) | -- |
| Age (years) | 14.4 (0.51) | 13.8 (0.90) | 15.8 (0.64) | 0.097 |
| Race, white† | 57 (53) | 18 (17) | 33 (31) | 0.18 |
| Duration of Diabetes (years) | 6.05 (0.51) | 3.25 (0.86) | 4.31 (0.62) | 0.04‡ |
| Serum C8 (ng/mL) | 59.9 (14.0) | 31.0 (25.1) | 89.0 (18.6) | 0.12‡ |
| Total Cholesterol (mg/dL) | 166.8 (4.43) | 170.2 (7.97) | 181.0 (5.98) | 0.061 |
| LDL Cholesterol (mg/dL) | 89.1 (3.43) | 95.1 (6.06) | 104.9 (4.55) | 0.0071 |
| VLDL Cholesterol (mg/dL) | 21.2 (1.89) | 29.2 (3.33) | 33.4 (2.50) | 0.0002 |
| HDL Cholesterol (mg/dL) | 53.7 (1.91) | 46.0 (3.43) | 42.7 (2.57) | 0.0010 |
| Triglycerides (mg/dL) | 127.2 (14.3) | 145.7 (25.7) | 166.5 (19.3) | 0.11 |
| White Blood Cell Count (x10e3/uL) | 6.86 (0.27) | 7.36 (0.49) | 8.81 (0.37) | <0.0001 |
| C-reactive Protein (mg/L) | 0.91 (0.59) | 1.60 (1.07) | 4.97 (0.80) | 0.0001 |
| Serum Creatinine (mg/dL) | 0.78 (0.02) | 0.74 (0.03) | 0.75 (0.02) | 0.30 |

*Age adjusted linear p-trend. †Percent based on row attribute, CMH test for linear trend across BMI categories. ‡Age adjusted quadratic p-trend.

**Figure 1. Percent of Individuals above 97.5th Percentile for Age and Sex Standardized Serum Lipid Biomarkers by Body Mass Index (BMI) Percentile**




*p-value <0.05 orthogonal polynomial contrast in logistic regression to test for quadratic trend across body mass index (BMI) categories.
†Percent of individuals below 2.5th percentile for high density lipoprotein cholesterol (HDLc).

**Table 3.** Number (%) of Individuals above 97.5th Percentile for Age- and Sex-Standardized Serum Lipid Biomarkers*

| | Total population |
|---|---|
| Total Cholesterol (mg/dL)l | 47 (41.2) |
| Triglycerides (mg/dL) | 60 (52.6) |
| HDL cholesterol (mg/dL) | 67 (58.8) |
| LDL cholesterol (mg/dL) | 52 (45.6) |
| White Blood Cell Count (x10e3/uL) | 46 (40.4) |
| C-reactive protein (mg/L) | 81 (71.1) |
| Serum Creatinine (mg/dL) | 48 (42.1) |

Values based on 2005-2006 NHANES data.

## Discussion

This study documents the prevalence of overweight and obesity and excess cardiovascular risk factors in an Appalachian population of children and adolescents with diabetes who had been exposed to environmental C8 contamination of drinking water. We observed a very high prevalence of overweight and obesity in our Appalachian pediatric population with diabetes. A significant material correlation between C8 and total and LDL cholesterol was observed among the highest category of BMI. Cardiovascular risk factors were more severe as BMI category increased.

In the entire C8-exposed pediatric population, which included those with and without diabetes, overweight/obesity and metabolic syndrome rates were higher than the national average (38 vs. 30% for overweight/obesity and 4.6 vs. 3.4% for the metabolic syndrome) [17]. The prevalence of overweight and obesity, (i.e. a BMI ≥85$^{th}$ percentile) in the C8-exposed population with diabetes, was 49%. This may be indicative not only of the high prevalence of overweight and obesity seen among those children with type 2 diabetes, but of the growing prevalence of overweight and obesity among children with type 1 diabetes. Data from the SEARCH for Diabetes study found a combined overweight and obesity prevalence of 31.5% among non-Hispanic white, 46.6% among African American, and 45% among Hispanic children with type 1 diabetes [18]. The prevalence of overweight and obesity in our almost exclusively White Appalachian population exceeds the prevalence in all three of those groups.

Levels of cardiovascular risk factors in our population appear to be elevated compared to similar populations of individuals of Type 1 or Type 2 diabetes. Triglyceride levels in obese children in our population were almost 1.5 times higher than that of TODAY youth aged 10-17 years with type 2 diabetes (166.5 vs 114.0 mg/dL). Our population, regardless of obesity status, had twice as many individuals with elevated triglycerides compared to youth in the TODAY study [19]. Although we did not see a significant increase in triglyceride levels across categories of BMI percentile, we did observe a significant quadratic trend in the prevalence of individuals with triglycerides above the 97.5$^{th}$ percentile as category of BMI percentile increased.

We observed a significant linear increase in LDL cholesterol across categories of BMI; however we observed a non-significant U-shaped trend across the percentage of those with LDL cholesterol levels greater than the 97.5$^{th}$ percentile across BMI categories. Dabelea et al [18] found a longitudinal association between increased LDL cholesterol and pulse wave velocity, which was used to measure the progression of arterial stiffness, in children with type 1 diabetes. In addition to the much higher levels of LDL cholesterol among our obese group (104.9 mg/dL), and even our overweight group (95.1 mg/dL), compared to values in the TODAY population (85.0-89.1 mg/dL) [19], the proportion of individuals with elevated LDL cholesterol (>97.5$^{th}$ percentile) in our study was also greater (45.6% vs. 4.5-10.7%). This is likely reflective of the differences in the racial distribution in the two populations (5% non-White in the C8 Health Study population vs. 80% non-White in the TODAY study, respectively). Non-Whites, in particular African American youth and adults, are generally reported to have lower lipid and triglyceride levels than Whites [20-22]. Nevertheless, the increased LDL cholesterol levels observed in our population suggests that Appalachian populations, such as ours, may exhibit a greater risk for cardiovascular disease than other populations with youth-onset diabetes.

In a previous study of all children and adolescents in the C8 health study, not specific for diabetes, no material correlations were found between serum C8 and levels of cardiovascular risk factors [17]. However, in this current study of the subpopulation with diabetes, we found significant, although not material, correlations between serum C8 and LDL cholesterol. Furthermore, the correlations appeared to strengthen among those with BMI >95$^{th}$ percentile, in which C8 was correlated with both total and LDL cholesterol. This evidence suggests that C8 exposure may be more detrimental for those in the highest weight categories, especially among children and adolescents with diabetes. Our findings are similar to those of Timmermann et al., who saw significant associations of exposure to polyfluorinated compounds with higher insulin and triglyceride concentrations among those that were overweight in a cross-sectional population of 8-10 year olds [23]. Given the small number of individuals in our study, our observation may also be purely due to chance. Longitudinal studies, with a larger number of subjects would be needed to determine the direction of the association between polyfluorinated compound exposure and diabetes among overweight children.

We observed a U-shaped relationship between BMI category

and cardiovascular risk factors such as triglycerides, HDL cholesterol, white blood cell count, and C-reactive protein levels. This U-shaped relationship has been seen between BMI and mortality within the general population [24], and among individuals with both Type 1 and Type 2 diabetes for many chronic diseases [25-28]. However, the relationship with cardiovascular disease, especially among children, is still not understood. Lewis et al. suggests that the relationship of overweight with cardiovascular disease may be influenced by the presence of cardiovascular risk factors [29].

This study was subject to several limitations. The small sample size limited more detailed analyses. We used self- or parent/guardian-reported height and weight for the calculation of BMI and BMI percentiles, as measured height and weight were unavailable in this population. Due to small sample sizes and missing data, we were unable to identify which type of diabetes mellitus individuals had. We did not have information on individual C8 exposure levels or to possible variable length of exposure. Universally recognized standardized cut-off points for cardiovascular risk factors have not yet been developed for children; therefore our use of values greater than the 97.5$^{th}$ percentile may not adequately represent the cardiovascular risk of this population or be directly comparable to results in different studies. Previous studies have used different cut-off points for cardiovascular risk factors such as levels of total cholesterol, LDL cholesterol, and triglycerides greater than the 95$^{th}$ percentile and HDL cholesterol less than the 5$^{th}$ percentile [30]. Additionally, serum creatinine was not collected for individuals in the NHANES population less than 12 years of age. To account for this in analysis, the age-and sex-adjusted 97.5$^{th}$ percentile for those who were aged 12 years was used as the cut-off point for everyone in our population <12 years, which may yield a conservative estimate of elevated serum creatinine for this population.

With up to 80% of adults with diabetes worldwide at risk for death from cardiovascular disease [31] and evidence that cardiovascular disease begins during childhood and adolescence and progresses into adulthood [30], the earlier onset of diabetes in our population may yield more aggressive cardiovascular outcomes [32]. It is imperative to reduce the increasing rate of cardiovascular risk factors in children with diabetes, risk factors that will likely be carried into adulthood. The results of this study indicate that this Appalachian population of children and adolescents with diabetes are at an increased risk for cardiovascular disease and emphasize the need for an understanding of the disparities within specific populations as well as for health interventions individualized for these different populations. Additionally, our results suggest a U-shaped relationship between BMI and cardiovascular disease risk factors in the pediatric population with diabetes, with the overweight category appearing to be protective against future cardiovascular disease. Further investigations will be necessary to determine if this is simply a marker of better glycemic control.

## Acknowledgments

Funding for this project was provided by The Eye Foundation of America and the Ross Foundation. BNC and PJM were also partially supported by a grant from the National Institutes of Health General Medical Sciences (U54GM104942).

The authors report no conflicts of interest.

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