Nicotine & Tobacco Research, 2018, 474–481
doi:10.1093/ntr/ntx115
Original investigation
Received June 28, 2016; Editorial Decision May 19, 2017; Accepted May 25, 2017

Original investigation

Serum Cotinine and Hemoglobin A_{1c} Among a National Sample of Adolescents Without Known Diabetes

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Abstract

Introduction: National data suggest tobacco smoke is positively associated with higher glycated hemoglobin (HbA_{1c}) among adults. Our objective was to examine the association between serum cotinine and HbA_{1c} among adolescents without known diabetes.

Methods: We assessed adolescents 12–19 years old ($N = 11\,550$) who participated in the 1999–2012 National Health and Nutrition Examination Survey. We applied sampling weights while performing multiple linear regression analyses.

Results: The prevalence of serum cotinine indicative of no tobacco smoke exposure (TSE, <0.05 ng/mL) was 43.2%, passive TSE (0.05–2.99 ng/mL) was 38.9%, and active TSE (>3 ng/mL) was 17.9% in our sample. Mean (± standard error) HbA_{1c} in participants with no TSE was 5.16% (±0.01), passive TSE was 5.16% (±0.01), and active TSE was 5.14% (±0.01). No differences in HbA_{1c} were found between TSE groups including sex, age, race/ethnicity, education, income, and physical activity or the fully adjusted model with waist circumference. We found cotinine × sex ($p = .01$) and cotinine × age ($p = .02$) interactions. There was an association between cotinine and HbA_{1c} for males but not females. Within males, participants with cotinine ≥3 ng/mL (5.26 ± 0.02) had higher mean HbA_{1c} than those with cotinine 0.05–2.99 ng/mL and <0.05 ng/mL (both 5.20 ± 0.01, $p \leq .02$). The negative association between age and HbA_{1c} was stronger for participants with cotinine ≥3 ng/mL than participants with cotinine <0.05 ng/mL.

Conclusion: No linear association was found between HbA_{1c} and serum cotinine in adolescents overall after adjusting for potential confounders. Differences between TSE groups were found in males. Future research in adolescents should examine chronic TSE over time to examine the potential for development of type 2 diabetes.

Implications: TSE has been associated with increased risk for the development of type 2 diabetes among adults. It is unclear if this relationship holds in adolescents. We examined the association between serum cotinine and HbA_{1c} in adolescents without known diabetes who completed the 1999–2012 National Health and Nutrition Examination Survey. Although no association was found between serum cotinine and HbA_{1c} overall while controlling for potential confounding factors, we observed interaction effects that are indicative of TSE influencing HbA_{1c} differentially by sex and age. Reducing TSE in adolescents should be a priority for future tobacco control efforts.

Introduction

Type 2 diabetes and tobacco smoke, including passive tobacco smoke exposure (TSE), remain leading causes of morbidity and mortality in the United States.[1,2] Despite national efforts to prevent and reduce smoking among adolescents,[3] over 3800 adolescents initiate smoking each day, and about 80% will continue smoking into adulthood.[4] Recent data indicate that 41.1% of high school students have tried cigarette smoking in their lifetime and 15.7% have smoked in the past month.[5] Further, approximately 9.6 million US adolescents aged 12–19 years are exposed to passive TSE annually.[6] Tobacco smoke and type 2 diabetes are cardiometabolic risk factors that contribute to the future risk of early mortality among adolescents and young adults.[7]

Tobacco smoke may increase the risk for the development of type 2 diabetes.[8,9] Studies have shown that the acute effect of smoking is associated with glucose intolerance and insulin resistance.[10,11] Whether tobacco smoke leads to transient or continuous elevations in blood glucose concentration remains unclear. Further, self-reported smoking in adults has been positively associated with higher levels of glycated hemoglobin (HbA_{1c}),[12] an objective index of average blood glucose values over the preceding 3 months.[13] Cotinine, the major proximate metabolite of nicotine, is an objective assessment of TSE for both smokers and nonsmokers compared to self-report smoking assessments.[14] Prior research has used this gold standard measure to examine the relationship between smoking and HbA_{1c} among adults with diabetes[15] and without diabetes.[16] One study conducted among children and adolescents with type 2 diabetes studied the association between cotinine and HbA_{1c},[17] but limited research has been published investigating the association between cotinine and HbA_{1c} in adolescents without known diabetes.

The purpose of this study was to examine the relationship between serum cotinine and HbA_{1c} in adolescents without known diabetes while controlling for a priori defined covariates (sex, age, race/ethnicity, education, income level, physical activity, and waist circumference). We assessed possible interaction effects between serum cotinine and the covariates listed earlier. Our hypothesis was that higher serum cotinine categories would be associated with higher HbA_{1c} in adolescents.

Methods

Participants and Procedures

We conducted a secondary data analysis of the 1999–2012 National Health and Nutrition Examination Survey (NHANES), a nationally representative, cross-sectional survey that continuously monitors the health status of adults and youth.[18] An institutional review board determined the current study as not human subjects' research and thus exempt from review.

NHANES uses a complex, multistage probability sampling design to select participants[18] and is unique, as it combines household interviews with laboratory and physical examination components, described elsewhere.[19] We combined seven successive continuous NHANES cycles and limited our analysis to participants 12–19 years old (n = 13 343) who were interviewed and had a physical examination. Adolescents with diagnosed diabetes were excluded if they self-reported that they had diabetes (n = 63), took insulin (n = 37) or antihyperglycemic pills to lower blood glucose (n = 11) at the time of the interview. Serum cotinine was used as an objective measure of TSE in our sample.[14] Thus, we further excluded participants with missing serum cotinine or missing HbA_{1c} (n = 1682); this resulted in 11 550 study participants eligible for analysis.

Measures

Our independent variable of interest was serum cotinine, a biological marker of active smoking and passive TSE.[14] Cotinine detection limits have changed over time; in 1999–2000, the limit of detection was 0.05 ng/mL. In 2001–2002, there were two limits of detection; 0.05 ng/mL and 0.015 ng/mL. For 2003–2004 and subsequent years, the limit of detection was 0.015 ng/mL. Similar to prior research[16] and as we are using a categorical designation of serum cotinine, we used the higher detection limit of cotinine < 0.05 ng/mL as the cut point for our lowest category, for consistency. To distinguish smokers from nonsmokers, we used the cut point of ≥3 ng/mL, since it is sensitive to nondaily or light smoking. The optimal cotinine levels recommended to define passive TSE is 0.05–2.99 ng/mL.[20] Thus, the serum cotinine categories used in our study were (1) < 0.05 ng/mL, (2) 0.05–2.99 ng/mL, and (3) ≥3 ng/mL. Our outcome measure was blood HbA_{1c} (%). This was primarily analyzed as a continuous variable but was also examined using the definition: < 5.7% for normal (no diabetes); 5.7%–6.4% for prediabetes; and ≥6.5% for diabetes.[21]

Demographic variables chosen a priori as covariates were sex, age, race/ethnicity, education, income level, physical activity, and waist circumference. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic, and other race. Education was categorized as those enrolled in middle school (6th–8th grade), those enrolled in high school (9th–12th grade), and > high school (i.e., high school graduates, those who passed a general education development [GED] test or equivalent, and those who completed more than high school). We categorized annual household income level as < $20 000/year, $20 000–$44 999/year, $45 000–$74 999/year, and ≥$75,000/year. Physical activity was categorized as no/light, moderate, and vigorous activity. The physical examination portion included a body measurement component where weight, height, and waist circumference were measured.[22] Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared. The Centers for Disease Control and Prevention's sex-specific BMI-for-age references were used to determine BMI z-scores (BMIZ) using the lambda, mu, and sigma method method.[23]

Statistical Analysis

All of our analyses used appropriate sampling weights to account for the complex NHANES design, survey nonresponse, and poststratification so that the estimates can be generalizable to the whole US adolescent population without known diabetes. We examined associations between all the covariates listed earlier and serum cotinine categories among all participants included in the present study. The continuous variables such as age, BMIZ, and waist circumference are reported as mean ± standard error (*SE*), and analyses of variance were performed to test hypotheses about the equality of these means. We also calculated the median and interquartile ranges for each cotinine category. The categorical variables are reported as the raw frequency with weighted proportion in parentheses, and the p values were derived from chi-square tests.

We calculated mean HbA_{1c} of participants according to serum cotinine categories in an unadjusted linear regression model, a model adjusting for BMIZ only, and another model adjusting for waist circumference only, in order to assess whether adjusting for these two variables provide the same results. For these models, we tested the differences in mean HbA_{1c} across serum cotinine categories. Research shows that smokers have a lower mean BMI but tend to have a larger waist circumference and higher abdominal fat compared to

nonsmokers.[25–27] As BMI is strongly associated with waist circumference, we adjusted for BMIZ and waist circumference separately in these models to examine whether the relationship between diabetes and waist circumference is stronger than BMI,[28–30] as waist circumference measures central adiposity which is associated with insulin resistance often seen in type 2 diabetes.[28]

We built three linear regression models to examine the relationship between serum cotinine categories and HbA_{1c}, the continuously distributed outcome variable. The first model was unadjusted and the second model was adjusted for sex, age, race/ethnicity, education, income level, and physical activity. In the third model, we adjusted for the covariates and included waist circumference to assess for potential mediating effects of this variable. We adjusted for physical activity since prior research indicates physically inactive adolescents are more likely to smoke than physically active adolescents.[24] We did not adjust for BMIZ in our multiple linear regression analyses, however, due to collinearity, since this variable is highly correlated with waist circumference. We also examined all possible two-way interactions between serum cotinine and the covariates. The final model only included statistically significant interactions ($p < .05$). We calculated the conditional mean (± *SE*) HbA_{1c} level for the statistically significant interactions, and *p* values were adjusted using the Tukey–Kramer method.

We used SAS statistical software version 9.4 (SAS Institute, Inc., Cary, NC) survey procedures to conduct our analyses, to account for the survey design. Statistical tests were two-sided, and $p < .05$ was considered statistically significant. Adjustment for multiple comparisons was done by the Tukey–Kramer method when making pairwise comparisons of serum cotinine level for adolescents.

Results

Our final sample consisted of 11 550 participants after applying exclusion criteria. The prevalence of serum cotinine < 0.05 ng/mL indicating no TSE was 43.2% ($n = 4471$), serum cotinine 0.05–2.99 ng/mL indicating passive TSE was 38.9% ($n = 4930$), and 17.9% of participants ($n = 1879$) had serum cotinine ≥3 ng/mL indicating active smoking. Further, the median of cotinine for the no TSE group was 0.02 ng/mL, the passive TSE group was 0.25 ng/mL, and the active TSE group was 76.85 ng/mL.

The mean age of participants was 15.48 years ($SE = 0.03$); 51.2% were males and 48.7% were females. The majority of participants were white (59.8%) followed by Hispanic origin (18.8%), black (14.6%), and 6.8% of participants were other race. Most participants were in middle school (6th–8th grade; 41.8%) or high school (9th–12th grade; 41.0%), and 17.2% were high school graduates, passed a GED test or equivalent, or completed more than high school. Regarding annual household income level, 18.4% had an income of < $20 000/year, 28.2% had an income of $20 000–$44 999/year, 21.6% had an income of $45 000–$74 999/year, and 31.8% had an income of ≥$75 000/year. The majority (67.9%) of adolescents reported that they engaged in vigorous physical activity, 16.5% engaged in moderate physical activity, and 15.6% engaged in none/light physical activity. Mean BMIZ of participants was 0.52 ($SE = 0.02$), and mean waist circumference was 81.51cm ($SE = 0.24$). Serum cotinine categories significantly differed by sex, mean age, race/ethnicity, education, income level, physical activity level, mean BMIZ, and mean waist circumference. Characteristics of participants by serum cotinine categories are described in Table 1. The median and the interquartile range for each of the three serum cotinine categories are reported in the last row of Table 1.

The majority of participants had HbA_{1c} < 5.7% (normal/no diabetes; $n = 10 983$; 96.2%), 3.7% had HbA_{1c} between 5.7% and 6.4% (prediabetic; $n = 545$), and 0.1% had HbA_{1c} ≥6.5% (diabetic; $n = 22$). There were no statistically significant differences in HbA_{1c} levels across serum cotinine categories in the unadjusted, BMIZ adjusted, or waist circumference adjusted models (Table 2). In Table 3, models for the association between serum cotinine category and HbA_{1c} while controlling for covariates are presented. In the unadjusted linear regression model, there was no statistically significant difference found for HbA_{1c} between serum cotinine categories. For the adjusted linear regression model without waist circumference and the fully adjusted model with waist circumference, no statistically significant differences were found between serum cotinine categories and HbA_{1c} among participants (see Table 3).

We found a statistically significant interaction effect of serum cotinine × sex on HbA_{1c} ($p = .01$) and another statistically significant interaction effect for serum cotinine × age ($p = .02$). Table 4 outlines the results of the model including means (*SE*) of HbA_{1c} according to serum cotinine category and sex and serum cotinine category by age.

We found a significant difference in mean HbA_{1c} between male participants with serum cotinine 0.05–2.99 ng/mL and serum cotinine ≥3 ng/mL ($p = .01$). Male participants with serum cotinine ≥3 ng/mL (5.26 ± 0.02) had significantly higher mean HbA_{1c} than male participants with serum cotinine 0.05–2.99 ng/mL (5.20 ± 0.01). Similarly, there was a statistically significant difference in HbA_{1c} between male participants with serum cotinine < 0.05 ng/mL and serum cotinine ≥3 ng/mL ($p = .02$). Male participants with serum cotinine ≥3 ng/mL (5.26 ± 0.02) had higher mean HbA_{1c} than male participants with serum cotinine < 0.05 ng/mL (5.20 ± 0.01). There were no statistically significant differences found based on mean HbA_{1c} between serum cotinine categories within females. Between male and female adolescents, there was a statistically significant difference found in the serum cotinine ≥3 ng/mL groups ($p = .001$). Specifically, male adolescents (5.26 ± 0.02) had significantly higher mean HbA_{1c} than female adolescents (5.19 ± 0.02) in this high TSE group. Further, the negative association between age and HbA_{1c} is stronger for participants with serum cotinine ≥3 ng/mL than participants with serum cotinine <0.05 ng/mL (see Table 4). Figure 1 shows this moderating effect and presents means of HbA_{1c} according to serum cotinine and the minimum age (i.e., 12 years old), mean age (i.e., 15.60 years old), and maximum age (i.e., 19 years old).

No statistically significant interaction effects were found between serum cotinine and the other covariates (i.e., race/ethnicity, education, income level, physical activity, and waist circumference).

Discussion

Despite evidence that tobacco smoke, including passive TSE, is associated with adverse cardiovascular complications and early mortality in adults,[7] minimal evidence exists as to whether elevated blood glucose (HbA_{1c}) is adversely affected by TSE among adolescents. We used a nationally representative sample of adolescents without known diabetes to examine the association between serum cotinine categories and HbA_{1c} in the current study. Using biochemically validated TSE, our findings in the overall sample did not support the hypothesis that higher TSE levels are associated with higher HbA_{1c} in a national sample of adolescents without known diabetes. This has been reported in a prior study of children with known diabetes.[17] A prior study[16] similar to ours of adults in the NHANES 1999–2008

Table 1. Characteristics of adolescents according to serum cotinine categories, NHANES 1999–2012[a]

Characteristics of study participants (N = 11 550)	All	Serum cotinine category			p
		<0.05 ng/mL (n = 4471)	0.05–2.99 ng/mL (n = 4930)	≥3 ng/mL (n = 1879)	
Age, mean (SE)	15.48 (0.03)	15.01 (0.05)	15.31 (0.05)	16.97 (0.06)	<.001
Sex					
Male	5902 (51.2)	2234 (40.4)	2482 (38.7)	1,186 (20.9)	<.001
Female	5648 (48.7)	2507 (46.2)	2448 (39.0)	693 (14.8)	
Race/ethnicity					
White	3043 (59.8)	1196 (43.0)	1153 (36.7)	694 (20.3)	<.001
Black	3461 (14.6)	817 (26.8)	2033 (56.6)	611 (16.6)	
Hispanic	4394 (18.8)	2408 (55.7)	1514 (32.9)	472 (11.4)	
Other race	652 (6.8)	320 (46.5)	230 (36.3)	102 (17.2)	
Education					
Middle school (grades 6–8)	4907 (41.8)	2350 (51.2)	2247 (41.8)	310 (7.0)	<.001
High school (grades 9–12)	4762 (41.0)	1794 (39.9)	1893 (35.9)	1075 (24.2)	
>High school	1875 (17.2)	595 (32.0)	786 (38.8)	494 (29.2)	
Household Income level					
<$20 000/y	2817 (18.4)	782 (25.3)	1400 (47.1)	635 (27.6)	<.001
$20 000–$44 999/y	3659 (28.2)	1455 (36.3)	1610 (43.4)	594 (20.3)	
$45 000-$74 999/y	2050 (21.6)	904 (44.4)	873 (40.4)	273 (15.2)	
>$75 000/y	2228 (31.8)	1307 (60.3)	682 (28.1)	239 (11.6)	
Physical activity					
None/light	1980 (15.6)	663 (34.2)	857 (37.3)	460 (28.5)	<.001
Moderate	1850 (16.5)	782 (43.3)	793 (39.4)	275 (17.3)	
Vigorous	7444 (67.9)	3,174 (45.1)	3,149 (39.0)	1,121 (15.9)	
BMIZ, mean (SE)	0.52 (0.02)	0.43 (0.03)	0.64 (0.03)	0.48 (0.04)	<.001
Waist circumference (cm), mean (SE)	81.51 (0.24)	79.55 (0.27)	82.35 (0.34)	84.46 (0.61)	<.001
Cotinine (ng/mL), median (IQR)	20.27 (1.12)[b]	0.02 (0.01–0.03)	0.25 (0.10–0.76)	76.85 (15.83–176.06)	—

Abbreviations: SE, standard error; IQR, interquartile ranges; BMIZ, body mass index z-scores using the Centers for Disease Control and Prevention's sex-specific BMI-for-age references; NHANES, National Health and Nutrition Examination Survey.

[a]Data are presented as mean (SE), n (weighted %) or median (IQR).

[b]Mean (*SE*).

sample suggested that a "dose–response" effect may be present, wherein there is a stronger association between HbA_{1c} in current smokers and in those with higher cotinine levels. After adjusting for all covariates, we found that serum cotinine was not significantly associated with HbA_{1c} among the combined sample of male and female adolescents. Although no significant interaction effects were found based on race/ethnicity, education, income level, physical activity, and waist circumference, we did find a significant serum cotinine × sex interaction effect among adolescents overall, suggesting that males with higher TSE levels (i.e., cotinine ≥3 ng/mL) have a significantly higher HbA_{1c} than females. As hypothesized, we also found a positive association within males, suggesting those with high TSE (i.e., cotinine ≥3 ng/mL) have significantly higher HbA_{1c} than males with no TSE (i.e., cotinine < 0.05 ng/mL) and passive TSE (i.e., cotinine 0.05–2.99 ng/mL). We also found a significant serum cotinine × age interaction effect, indicating that serum cotinine and age interact to moderate HbA_{1c}. Interestingly, our findings revealed the effects of TSE on HbA_{1c} are more pronounced for younger participants. Further research is needed to more thoroughly understand the complex influence sex and age have on the relationship between TSE and HbA_{1c}.

Since our study excluded known diabetes cases, these findings are concerning, given research indicates that the incidence and prevalence of type 2 diabetes among adolescents is increasing over time, underscoring a serious national concern for economic and health-care resources.[31] It is also important to note that the average age at diagnosis of type 2 diabetes has decreased from 52 years old to 46 years old over time.[32] Thus, more research is needed to explore potential relationships between TSE and glucose intolerance, especially since some adolescents had HbA_{1c} levels placing them at high risk of having or developing future diabetes.

Although it is well known that active smoking and passive TSE have numerous adverse health effects on adolescent health,[2] our study supports prior work that shows very high prevalence of TSE in youth. Our analysis indicates that 38.9% of the sample had serum cotinine levels consistent with passive TSE (i.e., 0.05–2.99 ng/mL) and 17.9% had serum cotinine levels consistent with active smoking (i.e., ≥3 ng/mL). Concerning cotinine levels indicative of active smoking, our findings align with prior national research[33] that used self-report measures and found participants who were older (M = 17 years old), white (20%), and male (21%) had high rates. Similar to previous research,[6] we also found that black participants (57%) and those with income <$20 000 per year (47%) had disproportionate rates of serum cotinine levels consistent with passive TSE. Overall, we found a negative relationship between household income level and serum cotinine level, which is not surprising given that individuals with lower socioeconomic status have significantly higher rates of smoking.[34] Further, expanding on prior work that found adolescents who are physically inactive are at increased risk of smoking,[24] we found that adolescents who were physically inactive or reported

Table 2. Mean HbA_{1c} of adolescents by serum cotinine categories, NHANES 1999–2012[a]

		Serum cotinine category			
HbA_{1c} (%)	*n*	< 0.05 ng/mL (*n* = 4471)	0.05–2.99 ng/mL (*n* = 4930)	≥3 ng/mL (*n* = 1879)	*p*
Unadjusted	11 550	5.16 (0.01)	5.16 (0.01)	5.14 (0.01)	.79
BMIZ adjusted	11 346	5.16 (0.01)	5.16 (0.01)	5.15 (0.01)	.82
Waist circumference adjusted	11 313	5.16 (0.01)	5.16 (0.01)	5.14 (0.01)	.43

Abbreviation: HbA_{1c}, glycated hemoglobin; BMIZ, body mass index *z*-scores using the Centers for Disease Control and Prevention's sex-specific BMI-for-age references; NHANES, National Health and Nutrition Examination Survey.
[a]Data presented as mean (*SE*).

Table 3. Association of HbA_{1c} according to serum cotinine categories in adolescents, NHANES 1999–2012

	Unadjusted (*N* = 11 550)		Multivariable adjusted without waist circumference[a] (*n* = 10 495)		Multivariable adjusted with waist circumference[b] (*n* = 10 318)	
Serum cotinine category	β Coefficient (*SE*)	*p*	β Coefficient (*SE*)	*p*	β Coefficient (*SE*)	*p*
<0.05 ng/mL	(Ref)		(Ref)		(Ref)	
005–2.99 ng/mL	−0.01 (0.04)	.86	−0.01 (0.01)	.41	−0.01 (0.01)	.13
≥3 ng/mL	−0.04 (0.06)	.53	0.01 (0.01)	.61	0.01 (0.01)	.85

Abbreviations: HbA_{1c}, glycated hemoglobin; Ref, reference group; NHANES, National Health and Nutrition Examination Survey.
[a]Adjusted for sex (male, female), age (continuous), race/ethnicity (white, black, Hispanic, and other race), education (middle school, high school, >high school), income level (<$20 000/y, $20 000–$44 999/y, $45 000–$74 999/y, > $75 000/y), and physical activity (none/light, moderate, and vigorous).
[b]Adjusted for sex, age, race/ethnicity, education, income level, physical activity, and waist circumference (continuous).

Table 4. Interaction effects based on sex and age according to serum cotinine categories in adolescents, NHANES 1999–2012

		Serum Cotinine Category			
HbA_{1c} (%)	*n*	<0.05 ng/mL (*n* = 4471)	0.05–2.99 ng/mL (*n* = 4930)	≥3 ng/mL (*n* = 1879)	*p* value Interaction
Sex					
Male	5902	5.20 (0.01)[a]	5.20 (0.01)[b]	5.26 (0.02)[c]	0.01
Female	5648	5.20 (0.01)	5.17 (0.01)	5.19 (0.02)	
Age	10 318	Ref	0.003 (0.004)[d]	−0.014 (0.006)	.02[e]
12 years old	—	5.25 (0.02)	5.23 (0.02)	5.32 (0.03)	
15.60 years old[f]	—	5.20 (0.01)	5.18 (0.01)	5.21 (0.01)	
19 years old	—	5.14 (0.02)	5.14 (0.01)	5.11 (0.02)	

Abbreviations: HbA_{1c}, glycated hemoglobin; Ref, referent; NHANES, National Health and Nutrition Examination Survey.
[a]Within males, the <0.05 ng/mL category has lower HbA_{1c} than the ≥3 ng/mL category; $p = .02$.
[b]Within males, the 0.05–2.99 ng/mL category has lower HbA_{1c} than the ≥3 ng/mL category; $p = .01$.
[c]Within the ≥3 ng/mL category, males have a higher HbA_{1c} than females; $p = .001$.
[d]β Coefficient (*SE*).
[e]Age had a significant interaction effect on HbA_{1c} for participants in the ≥3 ng/mL category compared to participants in the <0.05 ng/mL category.
[f]Mean age of participants (*n* = 10 318) included in the analysis.

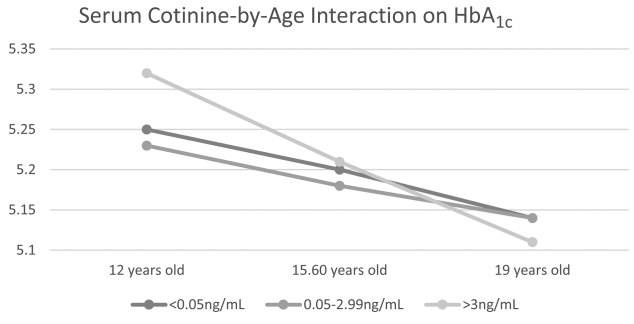

Figure 1. Interaction of serum cotinine with age. Line represents mean glycated hemoglobin (HbA_{1c}).

light physical activity had high rates of passive TSE (37%) and active TSE (29%). Similarly, we found that adolescents in the passive TSE group (*M* = 82 cm) and active TSE group (*M* = 85 cm) had higher waist circumferences than those in the no TSE group (*M* = 80 cm). This was expected, since it is well known that smokers tend to have a larger waist circumference and lower BMI.[25–27] Interestingly, however, we found that adolescents with the highest mean BMIZ were in the passive TSE group (*M* = 0.64). These findings underscore the continued critical need for passive TSE reduction and smoking cessation efforts among this age-group.

The present study's results differ from prior research conducted among adults without diabetes,[16] and this merits discussion. One potential reason our analyses did not find that higher

serum cotinine categories were associated with increased HbA_{1c} is that HbA_{1c} values and thus levels of glycemic control, as well as diabetes risk,[35] increase with age and active smoking and passive TSE.[36] In addition to a dose-dependent relationship, it is possible that there is a time-dependent relationship between smoking and glycemic control. Prior research indicates that HbA_{1c} significantly increases with number of cigarettes smoked per day and pack-years among current smokers compared to never smokers.[37] Several recent meta-analyses found a relationship between passive TSE and risk of type 2 diabetes,[38–40] indicating that the intensity and duration of TSE is associated with the risk of worse glycemic control. This suggests that adults may be more susceptible to increased HbA_{1c} due to their age and concomitant longer periods of either active smoking or passive smoking. Thus, adolescents may have limited, short-term exposure to active smoking and passive smoking compared to adults, and the latent duration of TSE in adolescents may not be long enough to measure the potential metabolic consequences of active smoking and passive smoking. Other research suggests possible mechanisms that may explain higher HbA_{1c} levels in adult smokers including nicotine-induced oxidative stress that contributes to pancreatic β-cell loss, mitochondrial dysfunction, and inflammation, which reduces insulin release and negatively affects insulin action and contributes to the development of insulin resistance.[41] Further, research found that intravenous infusion of nicotine aggravated insulin resistance in type 2 diabetic adult patients but not in healthy control participants.[42] Similarly, there is strong evidence that tobacco smoke, including passive TSE, increases cardiovascular disease development in patients with diabetes to a greater extent than in those without diabetes over time.[43] Finally, recent studies have found that in adult never smokers, passive TSE is positively associated with type 2 diabetes.[35,44] However, similar to our findings, Alshaaraway and Elbaz[44] found no association between those with levels of serum cotinine below 3 ng/ml and HbA_{1c} among never smokers.

Limitations

This study has several strengths. We examined the relationship between tobacco smoke and HbA_{1c} using biomarkers rather than relying on self-report measures. Our results are generalizable to the US adolescent population who do not have known diabetes, since we tested this relationship in a nationally representative sample. We controlled for several potential confounders that may affect the relationship between cotinine and HbA_{1c}. However, this study is not without limitations. Inferences are not causal due to the cross-sectional NHANES design. Residual confounding may exist and unexpectedly bias results although we adjusted for several potential confounders. However, we did not adjust for diet or alcohol consumption in our analyses, which may be confounders in the association between smoking and HbA_{1c}. Finally, the half-life of cotinine is 16–17 h and reflects short-term nicotine exposure and not chronic exposure over time;[14,45] additionally, serum cotinine alone does not assess the number of cigarettes that a nonsmoker has been passively exposed to nor is it enough to assess the pack-years of a smoker. Thus, the use of serum cotinine in this study did not assess or differentiate the effects that chronic nicotine exposure has on glycemic control. Therefore, the lack of information available on the intensity and duration of TSE is a limitation in the present study. Future research involving adolescents should seek to examine chronic TSE over time to further examine the association between HbA_{1c} and serum cotinine.

Conclusions

In sum, we assessed the relationship between serum cotinine and HbA_{1c} in a national sample of US adolescents. HbA_{1c} did not differ significantly overall based on serum cotinine category after adjusting for potential confounders. Contrary to findings in adults without diabetes,[16] these results did not support the hypothesis that tobacco smoke measured by serum cotinine, with a half-life of about 16–17 h,[14,45] leads to a direct increase in blood glucose levels in the overall sample as reflected by HbA_{1c}. However, we did find a statistically significant interaction effect that is indicative of TSE influencing HbA_{1c} differently in male adolescents versus female adolescents such that male adolescents with higher TSE levels (i.e., cotinine ≥3 ng/mL) have significantly higher mean HbA_{1c} than female adolescents. We also found that males with higher TSE levels had significantly higher HbA_{1c} than males with no TSE (i.e., cotinine <0.05 ng/mL) or passive TSE (i.e., 0.05–2.99 ng/mL). We also found a significant serum cotinine × age interaction which suggests the exposure effect on HbA_{1c} is more pronounced for younger adolescents. The present study's findings suggest that the association between HbA_{1c} and serum cotinine is complex and needs to take into account sex and age. Due to the relatively small sample size and cross-sectional nature of this study, it will be of interest to extend this research to a larger sample size and to longitudinally compare the complex relationship between serum cotinine and HbA_{1c}. If there is an association, it will be important to determine at what age this association is evident so that appropriate interventions can be put into place well before this point, given the disproportionately high prevalence of diabetes in adult populations.[8] Future research is also needed to determine whether this association occurs in certain subgroups so that targeted interventions can be developed.

Clinical guidelines for HbA_{1c} define prediabetes as 5.7%–6.4% and diabetes as 6.5% and above.[21] Our sample had relatively low mean HbA_{1c}. Prior studies have found a positive association between HbA_{1c} and age but conclude the difference may not be large enough to introduce age-specific reference guidelines.[36,46,47] Further examination is needed to determine whether age-specific criteria is appropriate, especially since the majority of participants had HbA_{1c} percentages below prediabetic levels. Thus, current cut points may underrate the prevalence of prediabetes. Although studies on adults suggest an association between type 2 diabetes and smoking,[8] more research is needed to identify why smoking affects HbA_{1c}, especially among nondiabetic individuals.[12] Future surveillance of tobacco smoke, including passive TSE, as a risk factor for high HbA_{1c} in adolescents may provide clarity into the reported type 2 diabetes trends found in adulthood. Furthermore, it is clear that longitudinal research is needed to determine the underlying mechanism, dose response, and timing in which the effect of TSE on HbA_{1c} in never smokers occurs. Our study findings further suggest the need for longitudinal research to explore these issues and the urgent need to continue to develop and test interventions to reduce TSE and active smoking in adolescence as a way to reduce the future development of type 2 diabetes in adulthood.

Funding

This work was supported by an Institutional Clinical and Translational Science Award, (NIH/NCATS grant number 8UL1TR000077-05); and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NIH grant number 1R01HD083354). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Declaration of Interests

None declared.

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