Published in final edited form as:

J Pediatr. 2014 July ; 165(1): 110–116. doi:10.1016/j.jpeds.2014.02.024.

Smoking and Arterial Stiffness in Youth with Type 1 Diabetes: The SEARCH CVD study

Amy S Shah, MD MS¹, Dana Dabelea, MD PhD², Jennifer W Talton, MS³, Elaine M Urbina, MD MS¹, Ralph B D'Agostino Jr³, R Paul Wadwa, MD⁴, Santica Marcovina, PhD⁵, Richard F Hamman, MD DRPH², Stephen R Daniels, MD PhD⁴, and Lawrence M Dolan, MD¹

¹Cincinnati Children's Hospital & University of Cincinnati, Department of Pediatrics, Cincinnati, OH USA 45229

²Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Aurora, CO USA 80045

³Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC USA 27157

⁴Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO USA 80045

⁵Northwest Lipid Research Laboratories, University of Washington, Seattle, WA USA 98195

Abstract

Objective—To evaluate the effects of smoking on early markers of cardiovascular (CV) disease (arterial stiffness) in adolescents with and without type 1 diabetes (T1D) in the SEARCH CVD study.

Study design—Participants included 606 youth [18.9 ± 3.3 years, 83% non-Hispanic white; 50% male]. Six groups were defined: (1) T1D smokers (n=80); (2) T1D former smokers (n=88); (3) T1D non-smokers (n=232); (4) non-T1D smokers (n=40); (5) non-T1D former smokers (n=51); and (6) non-T1D non-smokers (n=115). Arterial stiffness measurements included pulse wave velocity (PWV), augmentation index (AIX) and brachial distensibility (BrachD). Multivariate linear regression was used to assess the independent and joint effects of T1D and smoking on arterial stiffness.

Results—Nearly 20% of both T1D and non-T1D youth were smokers. In youth without T1D, smokers had higher trunk and arm PWV. After adjustment for potential confounders T1D but not smoking was an independent predictor of PWV ($p < 0.05$). Moreover, smoking status did not modify the association between T1D and increased arterial stiffness.

© 2014 Mosby, Inc. All rights reserved

Address correspondence/reprints: Amy S Shah MD MS Cincinnati Children's Hospital Medical Center. 3333 Burnet Ave ML 7012. Cincinnati Ohio 45226, amy.shah@cchmc.org, 513- 636-4744.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The authors declare no conflicts of interest.

Portions of the study were presented orally at the American Diabetes Association meeting.

Conclusions—We found a high prevalence of smoking among youth with and without T1D; however, smoking status was not independently associated with increased arterial stiffness in youth with T1D.

Keywords

pediatrics; cigarette; vascular disease; cardiovascular disease

Cross-sectional and prospective studies in adults with type 1 diabetes (T1D) have shown that cigarette smoking increases the risk of micro (1–4) and macrovascular complications (5; 6) and premature mortality (7). Although cigarette smoking is harmful at all ages, adolescents with T1D stand out as a particularly high-risk group given their increased risk to develop cardiovascular disease (8).

Prior work from has shown that adolescents with T1D have evidence of early arterial disease compared with their healthy counterparts (9–11). However, studies documenting the association between cigarette smoking and early arterial disease in adolescents with T1D are lacking. The purpose of this study was to evaluate the effects of smoking on early markers of arterial disease as measured by arterial stiffness.

Methods

Data for these analyses come from SEARCH Cardiovascular Disease, an ancillary study to the SEARCH for Diabetes in Youth Study, conducted at 2 clinical sites Ohio and Colorado. A detailed description of the SEARCH for Diabetes in Youth study has been previously published (12). Participants with T1D that were included in this analysis were age 11–26 years at the time of the study visit, diagnosed with T1D by a health care provider, and had T1D for at least 5 years. “Control” participants without T1D (fasting glucose <100 mg/dl) were recruited from primary care clinics in Colorado and Ohio and frequency-matched to T1D participants by age, race/ethnicity and sex.

Participants were seen at an in-person study visit where fasting blood samples were collected, processed and sent to the SEARCH Central Laboratory at the University of Washington for analysis of total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol, triglycerides, glucose and hemoglobin A1c (HbA1c) as previously described (12).

Weight and height were measured in light clothing without shoes. Height was measured to the nearest 0.1 cm and weight to the nearest 0.1 kg. The average of the two anthropometric measures was used in the analyses. Weight and height were compared with 2000 Centers for Disease Control and Prevention standards for the United States to calculate body mass index (BMI) Z scores. Blood pressure was measured using a standardized protocol. Participants were seated with feet resting flat on a surface and right arm resting at heart level. The first appearance of two consecutive beats determined the first Korotkoff phase (k1); the point at which a sound becomes muffled determined K4; and when the sound disappeared determined K5. K5 was used to define the diastolic blood pressure measurement. Blood

pressure was measured three times with the average used to calculate the mean systolic, diastolic and mean arterial blood pressure.

During the study visit participants also completed a study questionnaire which included several questions regarding cigarette smoking behaviors. Two questions were used to classify participants into “never”, “former”, and “current” smokers. If the participant answered “no” to the question “Have you ever tried cigarette smoking, even one or two puffs?” then the participant was classified as a “never” smoker. If the participant answered “yes” to the above question, they were asked “During the past 30 days, on how many days did you smoke cigarettes?” If the participant answered “none” then they were classified as a “former” smoker. If the participant answered “yes” to ever smoking a cigarette and said they had smoked at least one day in the past 30 days then they were classified as a “current” smoker.

Arterial stiffness was assessed by pulse wave velocity (PWV) using the SphygmoCor System (Atcor Medical, Sydney, Australia). A tonometer was used to collect proximal and distal arterial waveforms gated by the R-wave on a simultaneously recorded ECG. PWV was then calculated as the distance from the proximal artery to distal artery rounded to the nearest 0.1cm divided by the time delay measured between the feet of the two waveforms. Measurements were taken from the carotid artery to femoral artery (PWV trunk), the carotid artery to the radial artery (PWV arm), and the femoral artery to dorsalis pedis (PWV leg). Three separate recordings were taken at each site, averaged and are reported in m/sec (13). A higher PWV indicates stiffer vessels. Repeated measures of PWV have shown a coefficient of variability of < 7% (11).

Augmentation index (AIx), which is a mixed measure of central and peripheral stiffness was also collected using the SphygmoCor device. Pulse waves generated from the tonometer placed over the right radial artery were analyzed using a generalized transfer function that has been validated in the catheterization laboratory in adults to calculate a central aortic pressure wave (14). AIx is derived from the central pressure waveform by calculating the difference between the main outgoing wave and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure. Because AIx is affected by heart rate, values were adjusted to a standard heart rate of 75 beats per minute. A higher AIx implies stiffer vessels. Reproducibility studies have previously demonstrated intraclass correlation coefficients between 0.7 and 0.9 (11)

Three measures of BrachD, also a measure of peripheral arterial stiffness, were obtained with a DynaPulse Pathway instrument (PulseMetric, Inc., San Diego, CA). This device derives brachial artery pressure curves from arterial pressure distensibility signals obtained from a standard cuff sphygmomanometer. A lower BrachD indicates stiffer vessels. Repeated measures show coefficient of variability of < 9 % (11).

The SEARCH CVD study was reviewed and approved by local institutional review boards. Written informed consent and assent, where applicable, were obtained from all participants and their parent/guardian if aged <18 years at the time of the visit.

Descriptive statistics (mean (SD), median (IQR), n (%)) as appropriate) were calculated for the arterial stiffness measures and participant characteristics within each of the six groups (T1D smokers, T1D former smokers, T1D non-smokers, control smokers, control former smokers, and control non-smokers). General linear models were used to test for differences between the groups for each of the population characteristics and arterial stiffness measures; variables not normally distributed were transformed as needed. To examine the impact of smoking status on arterial stiffness in presence of T1D, we tested the interaction of smoking and T1D status on each of the arterial stiffness measures. Because the interaction was not significant we looked at the main effects of T1D and smoking status using multivariate generalized linear models with adjustments made for age, race, sex, blood pressure and heart rate, variables known to be highly associated with arterial stiffness, as well as clinic in order to account for any differences due to measurements being obtained at different sites (Ohio vs. Colorado). All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and p-values of < 0.05 were considered statistically significant.

Results

Table I presents the characteristics of the study participants by T1D and smoking status. Approximately 20% of adolescents with and without T1D were current smokers. P values in Table I represent differences across smoking groups among T1D and controls. Among youth with T1D, the three smoking groups differed in age, height, BMI z score, systolic blood pressure, triglycerides and HbA1c ($p < 0.05$). Pairwise comparisons (data not shown) for youth with T1D revealed that compared with T1D non-smokers, T1D former smokers were older, taller, and had higher systolic blood pressure and T1D current smokers were older, taller, with lower BMI z score and higher triglycerides and HbA1c values (all $p < 0.05$). T1D former and current smokers only differed in triglycerides and HbA1c, with current smokers having higher values compared with former smokers for both measures (both $p < 0.05$). Among the control group, the three smoking groups differed in age, weight, height, BMI and HbA1c ($p < 0.05$). Pairwise comparisons (data not shown) for control youth revealed that compared with control non-smokers, control former smokers had a lower HbA1c, were older and had a higher weight and BMI and control current smokers were older and had a higher weight, BMI and height (all $p < 0.05$). Control former and current smokers only differed in HbA1c with current smokers having higher HbA1c ($p < 0.05$). There were no differences in race, sex, duration of T1D, diastolic blood pressure, LDL or HDL cholesterol or fasting glucose across the three smoking groups in either T1D or controls.

Differences between T1D and controls within a smoking category are denoted with an asterisks (*) in Table I. T1D current smokers had higher total cholesterol levels compared with control current smokers ($p < 0.05$). T1D former smokers had a larger percentage that were NHW and had higher total and LDL cholesterol, and lower BMI compared with control former smokers, and T1D non-smokers had higher HDL cholesterol and lower triglycerides as well as a larger percentage that were NHW compared with control non-smokers (all $p < 0.05$). As expected for all smoking categories, T1D participants had higher HbA1c and fasting glucose compared with controls ($p < 0.05$).

Mean arterial stiffness measurements are shown in Table II. Similar to above, p values represent differences across smoking groups between T1D and controls. Among youth with T1D, the three smoking groups differed only in PWV trunk ($p<0.05$). Pairwise comparisons (data not shown) demonstrated increased PWV trunk in both T1D current and former smokers compared with T1D nonsmokers ($p<0.05$). In the control group, the three smoking groups differed in PWV trunk and PWV arm ($p<0.05$). Pairwise comparisons (data not shown) found that, compared with control non-smokers, current smokers had increased PWV arm ($p<0.05$) and former smokers had higher PWV trunk (all $p<0.05$). There were no differences in PWV leg, AIx, BrachD across the three smoking groups in either T1D or controls.

Comparisons among T1D and controls within a smoking category denoted with an asterisks (*) revealed T1D former smokers had a higher PWV leg compared with control former smokers and T1D non-smokers had higher AIx and lower BrachD compared with control non-smokers indicating increased arterial stiffness ($p<0.05$).

Multivariate linear models were constructed to determine whether T1D status and smoking status jointly or independently contributed to increased arterial stiffness (Table III). In models adjusted for age, race, sex, mean arterial blood pressure, heart rate and clinic site, the presence of T1D was an independent predictor of increased arterial stiffness as measured by higher PWV leg ($p<0.05$). However, smoking status was not a significant, independent determinant for any of the outcomes. Moreover, the interaction between smoking and T1D was not significant for any of the outcomes. We also re-ran our same models using a 2 group variable combining current and former smokers vs. non-smokers to determine if any smoking exposure was associated with increased arterial stiffness. Our results were unchanged; smoking status was not a significant independent determinant for any of the outcomes (data not shown).

Given that age and smoking status were highly correlated in our cohort (spearman correlation coefficient of $r_s=0.38$; average age of never smokers was 17.5 years whereas the former and current smokers was 20.5 years we suspected that age may be masking the relationship between smoking and arterial stiffness (Table I). In a sub-analysis, we matched current or former smokers to never smokers by age, race, sex, and T1D status and re-ran our adjusted models on this balanced group. There was still no association between smoking status and any of the arterial stiffness outcomes. For current and former smokers we also examined the association between the number of days smoked in the past 30 days (0-none, 1–19 days-some and >19 days-most) and arterial stiffness (using the same covariates as above). We found no association the number of days smoked in the past 30 days and arterial stiffness.

Discussion

We observed a high prevalence of smoking among youth with and without T1D. Our unadjusted data show that current and former T1D smokers and control smokers have increased arterial stiffness compared with non-smokers. However, in adjusted models that account for differences in age, race, sex, blood pressure and heart rate, we found that T1D only but not smoking was independently associated with measures of early arterial disease.

Moreover, smoking status did not modify the association between T1D and arterial stiffness measures. Therefore, these data suggest that although T1D is associated with an increased risk for early arterial disease, there is no added increase in arterial stiffness in youth with T1D who smoke.

Epidemiologic studies have established that cigarette smoke exposure is a major risk factor for cardiovascular disease (15). Cigarette smoking influences the initiation and progression of atherosclerosis by impairing vasodilation through decreased nitric oxide availability in the vessel wall (16), promoting inflammation through recruitment of leukocytes and pro-inflammatory cytokines (17), increasing LDL oxidation and formation of free radicals (18), and increasing hemostasis by promoting thrombosis (19) and decreasing fibrinolysis (20).

Similarly, diabetes increases the risk of cardiovascular disease as hyperglycemia is associated with increased thrombosis and inflammation (21). In addition, formation of oxidized atherogenic lipid particles (22), non-enzymatic glycosylation of proteins and lipids, and decreased nitric oxide availability in persons with T1D (23) all contribute to the accelerated development of atherosclerosis..

The independent effects of T1D on arterial stiffness are well established in both adults and youth (11; 24–26). Prior work in youth with T1D has shown who smoke display significantly worse metabolic control and a higher cardiovascular risk profiles (27). Therefore, in combination, smoking and diabetes are likely to impart detrimental effects on the vasculature. Prior work in adults with T1D has shown smoking is associated with arterial stiffness and nephropathy (mean age 26 years and 35 years, respectively) (28; 29), but to date the effects of smoking on early measures of arterial disease in younger populations (i.e. adolescents) has not been conducted.

In adults without T1D, the effects of smoking on arterial stiffness have shown mixed results. Even though some investigators have found that smoking for 6 years or more was associated with both central and peripheral arterial stiffness as measured by PWV and AIx (30–34), others have found no association. Rehill et al found that smoking was not associated with an increase in PWV trunk in men and women mean age 37.9 ± 11.4 years (35). Similarly, Yufu et al found no association with brachial ankle artery PWV in healthy adults (mean age 30 years) (36) and Taquet et al found no association with PWV trunk in healthy middle aged women (37). Lack of association between smoking and arterial stiffness in these studies was attributed to small cumulative tobacco consumption though participants smoked 10+ cigarettes per day (35; 36).

In this report, we studied current, former and non-smokers with and without T1D. This allowed us to examine the independent and joint effects of T1D and smoking. We found that even though T1D was independently associated with increased PWV, smoking was not. Although the reason for a lack of independent smoking effects on vascular stiffness in our study population is not clear, there are several potential explanations. First, the duration of smoking is likely to be relatively short, given the average age of our cohort. Second, the quantity of cigarettes smoked may be too small to have resulted in detectable effects on the vasculature. Work in adults has shown that the effects of smoking are acute and potentially

reversible with smoking cessation (38–41). Thus, it is plausible that the effects of smoking may be largely reversible in adolescents or that the vasculature in youth may be more resilient to the effects of smoking. Additionally, there may be a threshold effect of smoking (both in terms of dose and duration) at which accelerated vascular changes occurs. Lastly, the lack of association between smoking and arterial stiffness may be due to small sample size. However, post-hoc analyses demonstrated we were adequately powered to detect an association between smoking and an interaction with T1D and the vascular measurements.

We noted a high correlation between smoking status and age in our study. Smoking behaviors are known to increase with age (42). To account for this, we adjusted our models for age as well as conducted a sub-analysis matching current or former smokers to never smokers and still found no association between smoking status and arterial stiffness. It should be noted though that although this analysis accounted for differences in age, race, sex, and T1D status between smokers and non-smokers, it did not account for all potential cardiovascular risk factors or behaviors in this older group that may contribute to increased arterial stiffness.

Nearly 20% of participants in both the T1D and control groups were current smokers. These rates are similar to the national prevalence of smoking among youth in the US where it is estimated that 21% of people age 18–24 smoke (43). Although smoking cessation is recommended as part of all routine pediatric (44) and diabetes care visits (45), given the number of smokers in our study, it appears that the message, if at all delivered, is not being followed. In an elegant review recently published by Mays et al, the authors outline a comprehensive approach for behavioral intervention and prevention of smoking in youth with T1D (46).

There are some limitations of our study that should be discussed. We were unable to quantify pack years because we did not obtain the numbers of cigarettes smoked per day or the duration of smoking. We were also unable to account for the effects of passive smoking which could have effects on arterial stiffness measurements. Our data were cross sectional therefore we cannot comment on causation. Lastly, although our classification scheme to group smokers into three categories (never, former, current) smokers may have resulted in a heterogeneous former smoking group, the never and current smoking groups were clearly defined and we found no association between smoking and arterial stiffness in these two groups. Moreover, when the former and current smokers were classified into those that smoked on none, some, or most days, we still found no association between smoking and early arterial disease.

However, the main strengths of this study were the use of various vascular measurements to evaluate the potential associations with smoking. PWV trunk is the most robust measure of arterial stiffness (13). It is a central measure of arterial stiffness that predicts hard cardiovascular events in persons with and without diabetes even after adjustment for concurrent cardiovascular risk factors (47; 48). Both PWV arm and leg are less robust measures of arterial stiffness but were obtained because diabetes is known to affect the peripheral vasculature. AIx is a mixed peripheral and central vascular measure that represents a fraction of arterial stiffness function not represented by PWV. As well, it has

been shown to predict cardiovascular events (49). Finally, BrachD is a resting measure of vascular function in a medium muscular artery that is strongly related to cardiovascular risk factors (50). By using these various measurements, we aimed to test whether smoking had differential effects on the vasculature.

Cigarette smoking is a known major risk factor for the development of cardiovascular disease and its associated comorbidities. Smoking in the presence of T1D increases this risk in adults (1–6). Given the high prevalence of smoking among youth with T1D, smoking prevention and cessation should be advocated and discussed as part of each health care visit. Because the effects of smoking on the vasculature are not yet apparent in adolescents, even among those with T1D, smoking cessation efforts in youth are warranted and likely to be beneficial in terms of future cardiovascular health.

Acknowledgments

We are indebted to the many youth and their families and their health care providers, whose participation made this study possible. We also would like to thank the entire SEARCH for Diabetes in Youth investigators and study staff whose help was essential in moving this project forward.

Funded by National Institute of Diabetes and Digestive and Kidney Diseases (R01DK078542 to D.D.).

Glossary

(T1D)	Type 1 diabetes
(BMI)	Body mass index
(BP)	Blood pressure
(PWV)	Pulse wave velocity
(AIx)	Augmentation index
(BrachD)	Brachial distensibility

References

1. Chase HP, Garg SK, Marshall G, Berg CL, Harris S, Jackson WE, Hamman RE. Cigarette smoking increases the risk of albuminuria among subjects with type I diabetes. *JAMA*. 1991; 265:614–617. [PubMed: 1987411]
2. Couper JJ, Staples AJ, Cocciolone R, Nairn J, Badcock N, Henning P. Relationship of smoking and albuminuria in children with insulin-dependent diabetes. *Diabet Med*. 1994; 11:666–669. [PubMed: 7955992]
3. Mitchell BD, Hawthorne VM, Vinik AI. Cigarette smoking and neuropathy in diabetic patients. *Diabetes Care*. 1990; 13:434–437. [PubMed: 2318103]
4. Sawicki PT, Didjurgeit U, Muhlhauser I, Bender R, Heinemann L, Berger M. Smoking is associated with progression of diabetic nephropathy. *Diabetes Care*. 1994; 17:126–131. [PubMed: 8137682]
5. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. *Diabetologia*. 1991; 34:877–890. [PubMed: 1778353]
6. Yudkin JS. How can we best prolong life? Benefits of coronary risk factor reduction in non-diabetic and diabetic subjects. *BMJ*. 1993; 306:1313–1318. [PubMed: 8518573]
7. Moy CS, LaPorte RE, Dorman JS, Songer TJ, Orchard TJ, Kuller LH, Becker DJ, Drash AL. Insulin-dependent diabetes mellitus mortality. The risk of cigarette smoking. *Circulation*. 1990; 82:37–43. [PubMed: 2364522]

8. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, Parekh RS, Steinberger J. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular Disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. *Circulation*. 2006; 114:2710–2738. [PubMed: 17130340]
9. Haller MJ, Samyn M, Nichols WW, Brusko T, Wasserfall C, Schwartz RF, Atkinson M, Shuster JJ, Pierce GL, Silverstein JH. Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care*. 2004; 27:2911–2917. [PubMed: 15562206]
10. Jarvisalo MJ, Raitakari M, Toikka JO, Putto-Laurila A, Rontu R, Laine S, Lehtimäki T, Ronnemaa T, Viikari J, Raitakari OT. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. *Circulation*. 2004; 109:1750–1755. [PubMed: 15023875]
11. Urbina EM, Wadwa RP, Davis C, Snively BM, Dolan LM, Daniels SR, Hamman RF, Dabelea D. Prevalence of increased arterial stiffness in children with type 1 diabetes mellitus differs by measurement site and sex: the SEARCH for Diabetes in Youth Study. *J Pediatr*. 2010; 156:731–737. [PubMed: 20097360]
12. SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. *Control Clin Trials*. 2004; 25:458–471. [PubMed: 15465616]
13. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H. European Network for Non-invasive Investigation of Large A: Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006; 27:2588–2605. [PubMed: 17000623]
14. O'Rourke MF, Gallagher DE. Pulse wave analysis. *J Hypertens Suppl*. 1996; 14:S147–157. [PubMed: 9120672]
15. Freund KM, Belanger AJ, D'Agostino RB, Kannel WB. The health risks of smoking. The Framingham Study: 34 years of follow-up. *Ann Epidemiol*. 1993; 3:417–424. [PubMed: 8275219]
16. McVeigh GE, Lemay L, Morgan D, Cohn JN. Effects of long-term cigarette smoking on endothelium-dependent responses in humans. *Am J Cardiol*. 1996; 78:668–672. [PubMed: 8831402]
17. Mazzone A, Cusa C, Mazzucchelli I, Vezzoli M, Ottini E, Ghio S, Tossini G, Pacifici R, Zuccaro P. Cigarette smoking and hypertension influence nitric oxide release and plasma levels of adhesion molecules. *Clin Chem Lab Med*. 2001; 39:822–826. [PubMed: 11601680]
18. Ueyama K, Yokode M, Arai H, Nagano Y, Li ZX, Cho M, Kita T. Cholesterol efflux effect of high density lipoprotein is impaired by whole cigarette smoke extracts through lipid peroxidation. *Free Radic Biol Med*. 1998; 24:182–190. [PubMed: 9436629]
19. Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. *Vasc Med*. 1998; 3:21–28. [PubMed: 9666528]
20. Newby DE, Wright RA, Labinjoh C, Ludlam CA, Fox KA, Boon NA, Webb DJ. Endothelial dysfunction, impaired endogenous fibrinolysis, and cigarette smoking: a mechanism for arterial thrombosis and myocardial infarction. *Circulation*. 1999; 99:1411–1415. [PubMed: 10086962]
21. Creager MA, Luscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation*. 2003; 108:1527–1532. [PubMed: 14504252]
22. Napoli C, Triggiani M, Palumbo G, Condorelli M, Chiariello M, Ambrosio G. Glycosylation enhances oxygen radical-induced modifications and decreases acetylhydrolase activity of human low density lipoprotein. *Basic Res Cardiol*. 1997; 92:96–105. [PubMed: 9166989]
23. Williams SB, Goldfine AB, Timimi FK, Ting HH, Roddy MA, Simonson DC, Creager MA. Acute hyperglycemia attenuates endothelium-dependent vasodilation in humans in vivo. *Circulation*. 1998; 97:1695–1701. [PubMed: 9591763]
24. Brooks B, Molyneaux L, Yue DK. Augmentation of central arterial pressure in type 1 diabetes. *Diabetes Care*. 1999; 22:1722–1727. [PubMed: 10526742]

25. Llauro G, Ceperuelo-Mallafre V, Vilardell C, Simo R, Freixenet N, Vendrell J, Gonzalez-Clemente JM. Arterial stiffness is increased in patients with type 1 diabetes without cardiovascular disease: a potential role of low-grade inflammation. *Diabetes Care*. 2012; 35:1083–1089. [PubMed: 22357186]
26. Wilkinson IB, MacCallum H, Rooijmans DF, Murray GD, Cockcroft JR, McKnight JA, Webb DJ. Increased augmentation index and systolic stress in type 1 diabetes mellitus. *QJM*. 2000; 93:441–448. [PubMed: 10874053]
27. Hofer SE, Rosenbauer J, Grulich-Henn J, Naeke A, Frohlich-Reiterer E, Holl RW. Smoking and metabolic control in adolescents with type 1 diabetes. *J Pediatr*. 2009; 154:20–23. e21. [PubMed: 18804216]
28. Prince CT, Secrest AM, Mackey RH, Arena VC, Kingsley LA, Orchard TJ. Cardiovascular autonomic neuropathy, HDL cholesterol, and smoking correlate with arterial stiffness markers determined 18 years later in type 1 diabetes. *Diabetes Care*. 2010; 33:652–657. [PubMed: 20040653]
29. Hovind P, Rossing P, Tarnow L, Parving HH. Smoking and progression of diabetic nephropathy in type 1 diabetes. *Diabetes Care*. 2003; 26:911–916. [PubMed: 12610058]
30. Binder S, Navratil K, Halek J. Chronic smoking and its effect on arterial stiffness. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2008; 152:299–302. [PubMed: 19219224]
31. Levenson J, Simon AC, Cambien FA, Beretti C. Cigarette smoking and hypertension. Factors independently associated with blood hyperviscosity and arterial rigidity. *Arteriosclerosis*. 1987; 7:572–577. [PubMed: 3689203]
32. Mahmud A, Feely J. Effect of smoking on arterial stiffness and pulse pressure amplification. *Hypertension*. 2003; 41:183–187. [PubMed: 12511550]
33. Nakanishi N, Suzuki K, Kawashimo H, Nakamura K, Tatara K. Risk factors for the incidence of aortic stiffness by serial aortic pulse wave velocity measurement in middle-aged Japanese men. *Environ Health Prev Med*. 1998; 3:168–174. [PubMed: 21432498]
34. Nguyen QM, Srinivasan SR, Xu JH, Chen W, Berenson GS. Racial (black-white) divergence in the association between adiponectin and arterial stiffness in asymptomatic young adults: the Bogalusa heart study. *Am J Hypertens*. 2008; 21:553–557. [PubMed: 18292758]
35. Rehill N, Beck CR, Yeo KR, Yeo WW. The effect of chronic tobacco smoking on arterial stiffness. *Br J Clin Pharmacol*. 2006; 61:767–773. [PubMed: 16722843]
36. Yufu K, Takahashi N, Hara M, Saikawa T, Yoshimatsu H. Measurement of the brachial-ankle pulse wave velocity and flow-mediated dilatation in young, healthy smokers. *Hypertens Res*. 2007; 30:607–612. [PubMed: 17785928]
37. Taquet A, Bonithon-Kopp C, Simon A, Levenson J, Scarabin Y, Malmejac A, Ducimetiere P, Guize L. Relations of cardiovascular risk factors to aortic pulse wave velocity in asymptomatic middle-aged women. *Eur J Epidemiol*. 1993; 9:298–306. [PubMed: 8405315]
38. Centers for Disease Control. Health benefits of smoking cessation. *JAMA*. 1990; 264:1930.
39. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. *JAMA*. 2003; 290:86–97. [PubMed: 12837716]
40. Goldenberg I, Jonas M, Tenenbaum A, Boyko V, Matetzky S, Shotan A, Behar S, Reicher-Reiss H. Current smoking, smoking cessation, and the risk of sudden cardiac death in patients with coronary artery disease. *Arch Intern Med*. 2003; 163:2301–2305. [PubMed: 14581249]
41. Ockene JK, Kuller LH, Svendsen KH, Meilahn E. The relationship of smoking cessation to coronary heart disease and lung cancer in the Multiple Risk Factor Intervention Trial (MRFIT). *Am J Public Health*. 1990; 80:954–958. [PubMed: 2368857]
42. Bell RA, Mayer-Davis EJ, Beyer JW, D'Agostino RB Jr, Lawrence JM, Linder B, Liu LL, Marcovina SM, Rodriguez BL, Williams D, Dabelea D. Diabetes in non-Hispanic white youth: prevalence, incidence, and clinical characteristics: the SEARCH for Diabetes in Youth Study. *Diabetes Care*. 2009; 32(Suppl 2):S102–111. [PubMed: 19246575]
43. Vital signs: current cigarette smoking among adults aged ≥ 18 years--United States, 2005–2010. *MMWR Morb Mortal Wkly Rep*. 2011; 60:1207–1212. [PubMed: 21900875]
44. American Academy of Pediatrics. Policy statement--Tobacco use: a pediatric disease. *Pediatrics*. 2009; 124:1474–1487. [PubMed: 19841108]

45. Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. *Diabetes Care*. 2004; 27(Suppl 1):S74–75. [PubMed: 14693932]
46. Mays D, Streisand R, Walker LR, Prokhorov AV, Tercyak KP. Cigarette smoking among adolescents with type 1 diabetes: strategies for behavioral prevention and intervention. *J Diabetes Complications*. 2012; 26:148–153. [PubMed: 22494839]
47. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation*. 2002; 106:2085–2090. [PubMed: 12379578]
48. Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation*. 2010; 121:505–511. [PubMed: 20083680]
49. Vlachopoulos C, Aznaouridis K, O'Rourke MF, Safar ME, Baou K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis. *Eur Heart J*. 2010; 31:1865–1871. [PubMed: 20197424]
50. Urbina EM, Kiehlky L, Tsai J, Srinivasan SR, Berenson GS. Impact of multiple cardiovascular risk factors on brachial artery distensibility in young adults: the Bogalusa Heart Study. *Am J Hypertens*. 2005; 18:767–771. [PubMed: 15925733]

Table 1

Characteristics of SEARCH CVD participants, by T1D and smoking status

	T1D (n=400)				(Non T1D) Controls (n=206)			
	Current Smokers n=80	Former Smokers n=88	Non-Smokers n=232	p-value	Current Smokers n=40	Former Smokers n=51	Non-Smokers n=115	p-value
Age (years)	20.1(2.5)	20.4(2.9)	17.6(3.3)	<0.001	20.3(2.8)	21.2(2.7)	18(3.3)	<0.001
Race: n(% Non-Hispanic White)	71(88.8)	79(89.8)*	197(84.9)*	0.436	30(75)	39(76.5)	86(74.8)	0.973
Sex: n(% male)	47(58.8)	51(58)	112(48.3)	0.138	23(57.5)	23(45.1)	48(41.7)	0.226
Duration of T1D (years)	10.3(4.3)	9.9(3.6)	9.6(3.7)	0.303				
Weight (kg)	73.1(14.9)	72.8(14.8)	70(17.3)	0.090 [†]	80.1(26.2)	79.8(22.2)	69.6(18.8)	0.004 [†]
Height (cm)	172.2(9.7)	171.6(10.3)	168.7(10.9)	0.013	173.7(10)	171.9(8.9)	169.4(9.8)	0.039
BMI (kg/m ²)	24.7(5.1)	24.6 (4.1)*	24.4 (4.9)	0.857	26.5 (8.7)	27.0 (7.2)	24.0 (5.0)	0.010
BMI z-score:	0.4(1)	0.5(0.8)	0.7(0.9)	0.026	0.5(1.2)	0.7(1.1)	0.5(1)	0.582
Systolic BP (mmHg):	110(9)	113(11)	110(10)	0.029	111(12)	111(11)	110(10)	0.841
Diastolic BP (mmHg)	71(9)	70.4(9)	70(9)	0.883	68(10)	70(9)	69(8)	0.725
Total Cholesterol (mg/dl)	177(37)*	172(30)*	168(35)	0.060 [†]	164(30)	162(37)	163(28)	0.896 [†]
LDL Cholesterol (mg/dl)	101(33)	101(27)*	96(28)	0.181	93(26)	90(31)	94(24)	0.687
HDL Cholesterol (mg/dl)	52(13)	53(14)	54(14)*	0.304	49(16)	51(16)	49(12)	0.809
Triglycerides (mg/dl): median(25th, 75th)	94(69,132)	79(59,111)	76(56,109)*	0.001 [†]	83(60,127)	88(65,125)	86(63,115)	0.722 [†]
HbA1c (%)	9.7(1.7)*	8.8(1.8)*	8.7(1.7)*	<0.001	5(0.3)	4.9(0.3)	5(0.3)	0.017
Fasting glucose (mg/dl):	218(137)*	193(92)*	198(86)*	0.201	90.7(8.2)	87.2(6.7)	89.2(7.2)	0.070

Data are mean (standard deviation) unless noted. Overall p value indicates differences across smoking groups;

* indicates significant difference (p<0.05) between T1D and controls within a smoking category.

[†] based on log-distribution

Table 2

Arterial Measures by T1D and smoking status

	T1D (n=400)			(Non T1D) Controls (n=206)				
	Current Smokers n=80	Former Smokers n=88	Non-Smokers n=232	p-value	Current Smokers n=40	Former Smokers n=51	Non-Smokers n=115	p-value
PWV trunk (m/s)	6.0(0.9)	5.9(0.8)	5.7(0.9)	0.0042	5.7(0.8)	5.9(1.0)	5.5(0.7)	0.0085
PWV leg (m/s)	8.5(1.6)	8.4(1.4)*	8.1(1.3)	0.0696	8.2(1.5)	7.9(1.3)	7.8(1.3)	0.3561
PWV arm (m/s)	7.3(1.2)	7.3(1)	7.2(1)	0.5545	7.5(1.1)	7.3(1.4)	7.0(1.0)	0.0249
AIx (%)	0.1(10.9)	-0.9(10.6)	0.6(10.7)*	0.5548	-3.6(9.3)	-0.3(9.7)	-3.7(10.7)	0.1412
BrachD (%change/mmHg)	6.3(1.1)	6.4(1.2)	6.2(1.2)*	0.4033	6.5(1.5)	6.5(1.3)	6.5(1.3)	0.9842

Data are mean (standard deviation) unless otherwise noted. Overall p value indicates differences across smoking groups;

* indicates significant difference ($p < 0.05$) between T1D and controls within a smoking category.

Table 3
Determinants of increased arterial stiffness measures from multiple linear regression models

	PWV trunk (m/s)		PWV leg (m/s)		PWV arm (m/s)		AIx (%) [†]		BrachD (% change/mmHg)	
	Beta(SE)	p-value	Beta(SE)	p-value	Beta(SE)	p-value	Beta(SE)	p-value	Beta(SE)	p-value
Age	0.108(0.01)	<0.001	0.105(0.02)	<0.001	0.062(0.01)	<0.001	0.159(0.13)	0.2380	0.003(0.02)	0.8280
Race	-0.251(0.08)	0.002	-0.176(0.14)	0.2157	-0.522(0.11)	<0.001	-2.113(1.05)	0.0448	-0.019(0.13)	0.8816
Sex	0.091(0.06)	0.153	-0.206(0.11)	0.0721	-0.001(0.09)	0.9947	0.293(0.99)	0.7677	0.757(0.10)	<0.001
Mean Arterial Pressure	0.032(0.004)	<0.001	0.028(0.01)	0.0002	0.019(0.01)	0.0006	0.135(0.05)	0.0126	-0.023(0.01)	0.0003
Heart Rate	0.012(0.003)	<0.001	0.010(0.005)	0.0478	0.016(0.004)	<0.001	0.211(0.04)	<0.001	-0.020(0.004)	<0.001
T1D	0.083(0.06)	0.2020	0.290(0.12)	0.0131	0.013(0.09)	0.8804	1.282(0.85)	0.1321	-0.046(0.10)	0.6530
Smoking		0.8140		0.7847		0.5974		0.5004		0.2511
Current	0.051(0.08)		0.038(0.14)		0.050(0.11)		1.192(1.03)		0.200(0.12)	
Former	0.023(0.08)		-0.071(0.14)		0.106(0.10)		0.619(1.01)		0.119(0.12)	
Never	Reference		Reference		Reference		Reference		Reference	

Models adjusted for age in years, race (non-Hispanic white vs. other), sex (female vs. male), mean arterial blood pressure (mmHg), heart rate (beats per minute), T1D (yes vs. no), clinic site (Ohio vs. Colorado) and smoking (never vs. former, current).

[†] Height included in the model for AIx.