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Research

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Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study

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Abstract

Objective To assess whether active and passive smokers are more likely than non-smokers to develop clinically relevant glucose intolerance or diabetes.

Design Coronary artery risk development in young adults (CARDIA) is a prospective cohort study begun in 1985-6 with 15 years of follow-up.

Setting Participants recruited from Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California, USA.

Participants Black and white men and women aged 18-30 years with no glucose intolerance at baseline, including 1386 current smokers, 621 previous smokers, 1452 never smokers with reported exposure to secondhand smoke (validated by serum cotinine concentrations 1-15 ng/ml), and 1113 never smokers with no exposure to secondhand smoke.

Main outcome measure Time to development of glucose intolerance (glucose ≥100 mg/dl or taking antidiabetic drugs) during 15 years of follow-up.

Results Median age at baseline was 25, 55% of participants were women, and 50% were African-American. During follow-up, 16.7% of participants developed glucose intolerance. A graded association existed between smoking exposure and the development of glucose intolerance. The 15 year incidence of glucose intolerance was highest among smokers (21.8%), followed by never smokers with passive smoke exposure (17.2%), and then previous smokers (14.4%); it was lowest for never smokers with no passive smoke exposure (11.5%). Current smokers (hazard ratio 1.65, 95% confidence interval 1.27 to 2.13) and never smokers with passive smoke exposure (1.35, 1.06 to 1.71) remained at higher risk than never smokers without passive smoke exposure after adjustment for multiple baseline sociodemographic, biological, and behavioural factors, but risk in previous smokers was similar to that in never smokers without passive smoke exposure.

Conclusion These findings support a role of both active and passive smoking in the development of glucose intolerance in young adulthood.

Introduction

Tobacco use has long been known to be a major risk factor for cardiovascular disease,[1] and recent studies have identified a positive association between smoking and incidence of diabetes.[2–6] The evidence that smoking is an independent risk factor for the development of diabetes is still considered preliminary.[7] Some studies have shown a dose-response association between smoking and incidence of diabetes,[4 5] but others have not.[2] Also, some earlier prospective research failed to find an increased risk of diabetes among tobacco users.[8 9]

Several hypotheses have been proposed to link tobacco use and incidence of diabetes. Smoking has been linked to impaired response to glucose tolerance tests and insulin resistance.[10 11] Although smoking cessation can result in modest weight gain,[2] smoking is related to a more unhealthy distribution of upper body weight and greater waist:hip ratio.[12] Smoking has also been associated with risk of chronic pancreatitis and pancreatic cancer, suggesting that tobacco smoke may be directly toxic to the pancreas.[13]

Previous studies have used only self report, were not validated by biological measures such as cotinine, and have not considered people with passive (secondhand) exposure to tobacco. Also, previous studies have not included high proportions of African-Americans, a population at particular risk of developing diabetes.[14] We used a population based longitudinal study of African-American and white young adults in four US cities to evaluate the association of smoking and passive tobacco smoke exposure with risk of incident glucose intolerance (impaired fasting glucose or diabetes) and to explore potential causes of risk, including body weight distribution, insulin resistance, and inflammation, by using stratified and multivariate analyses. We hypothesised that current smokers would have a higher incidence of impaired fasting glucose and diabetes during follow-up than never smokers and that people exposed to passive tobacco smoke would have an intermediate risk.

Methods

Study design, participants, and measurements

The coronary artery risk development in young adults (CARDIA) study is an ongoing prospective, multicentre study of the natural history of the development of cardiovascular risk from young adulthood to midlife. In 1985-6, 5115 black and white men and women aged 18-30 years were recruited by random selection of telephone numbers from designated census tracts in Birmingham, Alabama; Chicago, Illinois; and Minneapolis, Minnesota, and by random selection from the membership list of a healthcare plan in Oakland, California. Only one participant per household was recruited, and the sampling scheme was designed to achieve a balance at each of the four sites by race (black, white), sex, education (high school degree or less, more than high school), and age (18-24 years, 25-30 years). The baseline examination lasted four to five hours and included blood pressure and anthropometric measurements, phlebotomy for chemistries and lipids, urine collection, lung function tests, and structured questionnaires on sociodemo-

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graphics, medical and family history, psychosocial characteristics, and nutrition, among others. More detailed descriptions of the sampling plan and initial cohort characteristics are available elsewhere.[15 16]

Participants were contacted by telephone every year and seen in person 2, 5, 7, 10, and 15 years after baseline for examinations of similar length and slightly variable content, although the protocols for collection of key data elements remained constant over time; re-examination rates among surviving cohort members were 91%, 86%, 81%, 79%, and 74% at the five time points. Thus, 1321 (26%) of the original 5115 participants were lost to follow-up by year 15.

Of 5115 CARDIA participants, 4903 had at least one follow-up examination (212 participants never returned for any follow-up examination and were excluded). For our analysis, we further excluded 246 participants who had serum glucose level ≥100 mg/dl or were on antidiabetic drugs or did not have baseline data on tobacco exposure, leaving 4657 participants with at least one follow-up examination in the dataset.

Definition of baseline tobacco exposure (main independent variable)

Tobacco exposure was ascertained at all years through a questionnaire administered by an interviewer.[17] Participants self reported current smoking, defined as regular cigarette smoking (at least five cigarettes a week almost every week for at least three months) at the time of a CARDIA examination. Previous smokers were those who, at baseline, reported previously using cigarettes but denied current smoking. Those who denied smoking at baseline were also asked about history of passive exposure to tobacco smoke.

A biochemical marker of nicotine uptake, serum cotinine, was also measured at baseline. Baseline self report of current cigarette smoking was validated against cotinine, and misclassification was found to be low (1.3% under-reporting overall).[18] For participants who self reported being never smokers at baseline, the tobacco exposure variable was defined as never smokers with positive passive smoke exposure if participants reported having had passive tobacco smoke exposure and they also had low cotinine concentrations (1-15 ng/ml) or never smokers with negative passive smoke if participants denied passive smoke exposure and cotinine was not detectable (0 ng/ml). In CARDIA analyses, cotinine concentrations over 15 ng/ml have been used to identify current smokers who denied smoking during the survey.[18] Because of this, we excluded from the analysis a small number of participants (n=85) who reported passive smoke but had cotinine levels >15 ng/ml and were thus probably misclassified current smokers,.

We thus divided 4572 participants into the four categories of tobacco exposure by using this combination of self report and serum cotinine measures at baseline: baseline current smokers, previous smokers, never smokers with exposure to passive smoke, and never smokers without reported passive smoke exposure.

Definition of outcomes

For our main analysis, the outcome was time to development of glucose intolerance. Fasting serum glucose was obtained at 7, 10, and 15 years during follow-up. Guidelines from the American Diabetes Association define impaired fasting glucose as serum glucose ≥100 mg/dl and <126 mg/dl and diabetes as fasting serum glucose ≥126 mg/dl (or ≥6.93 mmol/l). We defined development of glucose intolerance as having guideline defined impaired fasting glucose or diabetes, or report of being prescribed antidiabetic drugs, at any of the year 2, 5, 7, 10, or 15 examinations.

Covariates and potential mediating variables

The CARDIA database contains important sociodemographic, health behaviour, physical examination, laboratory, and health service related variables. Some variables were collected at baseline, and others were collected at baseline and during follow-up. Unless stated otherwise, we used baseline covariates for the purpose of this analysis.

Baseline sociodemographic factors included self reported ethnicity, age, sex, and years of education. Moderate alcohol consumption has been inversely associated with risk of developing diabetes.[3] Mean daily ethanol intake was calculated by using the following formula: mean ml ethanol per day = (usual number of 12 oz beers per week/7) × 16.7 ml + (usual number of 5 oz glasses of wine per week/7) × 17.02 ml + (usual number of 1.5 oz distilled spirits per week/7) × 19.09.[19]

Self reported food intake was recorded as total calories of food intake and total calories from fat per day. Physical activity was measured by using the interviewer based CARDIA physical activity history, which covers 13 different types of vigorous and moderate intensity activities. The physical activity score was calculated in exercise units reflecting the frequency and duration of activity over the previous year.[20]

Number of pack years smoked was also collected at baseline and all follow-up years. Baseline and follow-up physical examination data included systolic blood pressure and hip and waist circumference. Baseline and follow-up laboratory data included serum insulin and serum triglycerides, a marker of the metabolic syndrome that precedes diabetes. Additional prospective survey data collected from year 5 included household income, having health insurance, and number of physician visits. We included these variables as time dependent covariates.

On the basis of previous research, we postulated that baseline serum insulin concentrations, as a marker for insulin resistance, and waist:hip ratio, as a marker for central adiposity, might mediate any association of tobacco smoke and risk of diabetes. Serum C reactive protein, as a measure of inflammation, was not available at baseline, but was available at year 7. We assessed the impact of these variables on the main hypothesis after first adjusting for those variables that we considered potential confounding covariates.

Data analysis

The major independent variable was tobacco exposure at baseline. We first made individual comparisons for differences in covariates for each category of tobacco exposure. The comparison group was always never smokers with no passive smoke exposure, and we used *t* tests and χ^2 as appropriate. Similarly, we used *t* tests and χ^2 as appropriate to assess the association of tobacco exposure with possible variables within the causal pathway between tobacco and risk of diabetes (waist:hip ratio, serum insulin during follow-up, and C reactive protein at year 7).

To determine whether current smoking, previous smoking, and passive exposure to tobacco smoke were related to a greater risk of development of glucose intolerance, we used Kaplan-Meier analysis to assess the incidence of glucose intolerance. We compared the incidence of glucose intolerance by tobacco exposure at baseline by using log rank tests. We also subsequently used additional Kaplan-Meier curves to assess the incidence of diabetes.

We developed multivariate Cox proportional hazards models to adjust the association between levels of smoke exposure and

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incidence of glucose intolerance for various potential confounders. Exploratory analysis confirmed the appropriateness of modelling continuous variables as linear. The initial model included sociodemographic factors: ethnicity, sex, age, years of education, and income (time dependent). We then developed additional models to include physical and laboratory covariates (systolic blood pressure, serum triglycerides), health behaviours (physical activity, alcohol intake, total and saturated fat intake), and health service related variables (number of physician visits per year, (time dependent) health insurance status). The next model (reported below as the primary model) included all the covariates listed above that were found to differ significantly by tobacco exposure and was further adjusted for time dependent change in smoking (stopping or starting). We then repeated these analyses with diabetes (defined as fasting serum glucose >126 mg/dl or prescribed antidiabetic drugs) as the outcome.

We also introduced potential mediating factors (baseline waist:hip ratio and insulin concentration, year 7 C reactive protein) into subsequent models to evaluate for further attenuation of the main effect. To evaluate the potential dose-response effect of greater smoke exposure, we did an analysis using time dependent number of pack years smoked as a continuous main independent variable in additional models adjusted as for those described above.

Results

Among the 4572 participants, we identified a total of 1386 current smokers at baseline, 621 previous smokers, 1452 never smokers with reported passive tobacco smoke exposure or cotinine concentration 1-15 ng/ml, and 1113 never smokers with no passive tobacco smoke exposure reported (table 1). The 1386 current smokers smoked a mean of 10 (SD 8.7, range 0-62.5) cigarettes a day. The 1452 never smokers with positive passive smoke were exposed to a mean of 12.6 (SD 18.0) hours of smoke a week. At baseline, the mean age of participants was 25 (SD 3.6) years, 2529 (55%) were women, and 2283 (50%) were African-American. Smokers and never smokers with passive smoke exposure were more likely to be African-American and less likely to be women than were never smokers with no passive smoke exposure (table 1). Current smokers also had lower education, drank more alcohol, and had higher fat intake compared with never smokers with no passive smoke.

Table 1 Baseline characteristics of 4572 CARDIA participants by baseline (1985-6) tobacco exposure. Values are mean (SD) unless stated otherwise

Characteristic	Current smokers (n=1386)	Previous smokers (n=621)	Never smokers, passive smoke exposure (n=1452)	Never smokers, no passive smoke (n=1113)
Baseline age (years)*†	25 (3.6)	26 (3.2)	24 (3.7)	25 (3.6)
No (%) African-American*†‡	773 (56)	207 (33)	856 (59)	453 (41)
No (%) women‡	729 (53)	359 (58)	781 (54)	660 (59)
No (%) with less than high school education*†‡	789 (57)	213 (34)	508 (35)	245 (22)
No (%) with income at least $35 000*†‡	379 (32)	264 (48)	548 (43)	557 (55)
Baseline physical activity score	403 (294)	438 (284)	426 (316)	415 (285)
Baseline daily total caloric intake (kcal)*†‡	3365 (2063)	2685 (1308)	2880 (1514)	2548 (1393)
Baseline daily saturated fat caloric intake (kcal)*‡	55 (37)	42 (25)	46 (27)	40 (27)
Baseline alcohol consumption (ml/day)*†‡	20 (31)	13 (19)	8 (15)	6 (10)
Baseline systolic blood pressure (mm Hg)*	110 (11)	109 (11)	111 (11)	110 (11)
Baseline triglycerides (mmol/l)*†‡	0.85 (0.55)	0.81 (0.57)	0.74 (0.45)	0.73 (0.42)
Physician visits per year	1.6 (0.5)	1.7(0.5)	1.7 (0.5)	1.7 (0.5)
No (%) with health insurance*†‡	803 (73)	416 (81)	996 (83)	861 (88)
Baseline waist:hip ratio*†‡	0.79 (0.07)	0.77 (0.07)	0.77 (0.07)	0.77 (0.07)
Baseline serum insulin‡	9.9 (7.0)	10.2 (7.7)	11.4 (8.2)	10.8 (8.1)
C reactive protein at seven year follow-up‡	3.4 (6.7)	3.2 (16)	2.6 (3.6)	2.5 (4.6)

All variables measured at baseline (1985-6), except for income measured at year 5 and health insurance measured at year 7.
*P<0.05 for never smokers with passive smoke exposure versus never smokers with no passive smoke exposure.
†P<0.05 for previous smokers versus never smokers with no passive smoke exposure.
‡P<0.05 for current smokers versus never smokers with no passive smoke exposure.

Incidence of glucose intolerance and smoking or tobacco smoke exposure

In Kaplan-Meier analysis, overall incidence of glucose intolerance was 9.2% (95% confidence interval 8.4% to 10.1%) at 7 years of follow-up, 12.8% (11.9% to 13.9%) at 10 years, and 16.7% (15.5% to 17.8%) at 15 years. Fifteen year Kaplan-Meier incidence of diabetes during follow-up was 3.1% (2.6% to 3.7%). Across categories of tobacco exposure, 15 year incidence of glucose intolerance was greatest among current smokers and lowest among never smokers with no exposure to passive smoke (table 2). Never smokers with exposure to passive tobacco smoke had an intermediate incidence. The risk of previous smokers was statistically similar to that of never smokers with no passive smoke exposure.

In the primary Cox proportional hazards model, current smokers had a higher risk of glucose intolerance than never smokers with no passive smoke exposure, after adjustment for baseline sociodemographic factors (age, sex, race, years of education, family income (year 5)) and for baseline biological and behavioural factors—systolic blood pressure, triglycerides, alcohol consumption, body mass index, and change in smoking (starting for never smokers and previous smokers and stopping for current smokers) collected during follow-up (table 3). Never smokers with positive passive smoke exposure also had a greater risk of developing glucose intolerance, compared with never smokers with no positive passive smoke after adjustment.

In a separate proportional hazards model, the unadjusted point estimate of the risk of development of diabetes was 1.58 (95% confidence interval 0.94 to 2.63) for smokers and 1.40 (0.84 to 2.33) for never smokers with positive passive smoker exposure, compared with never smokers with no passive smoke exposure. Further adjustment for variables as in the primary model did not alter the significance or direction of these results.

Pack years as a marker for amount of tobacco exposure

Consistent with our primary analysis, increasing pack years of smoking over time among the 4572 participants was associated with an increased risk of developing glucose intolerance. After adjustment, for every increase in 10 pack years of smoking the risk of developing glucose intolerance increased by 18% (hazard ratio 1.18, 1.02 to 1.36).

Incidence of glucose intolerance by race-sex subgroups

Incidence of glucose intolerance by tobacco exposure varied among race-sex subgroups (table 4). The association between current smoking and glucose intolerance seemed to be stronger in white people than in black people for both women and men ($P < 0.001$ for overall interaction with race-sex).

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Table 2 Prospective 5, 7, 10, and 15 year incidences (percentages) of glucose intolerance by baseline tobacco exposure: CARDIA study, 1985-2001

Interval	Never smokers, no passive smoke exposure		Never smokers, passive smoke exposure		Previous smokers		Current smokers	
	No*	Incidence (95% CI)†	No*	Incidence (95% CI)†‡	No*	Incidence (95% CI)†§	No*	Incidence (95% CI)†‡
5 year	1077	0.3 (0 to 1)	1390	0.1 (0 to 1)	593	0.3 (0 to 1)	1303	0.1 (0 to 1)
7 year	1044	6 (5 to 8)	1338	9 (7 to 10)	563	8 (6 to 10)	1237	13 (11 to 15)
10 year	930	10 (8 to 11)	1164	13 (11 to 15)	485	12 (9 to 15)	1016	16 (14 to 19)
15 year	828	11 (10 to 14)	981	17 (15 to 19)	414	14 (12 to 18)	801	22 (19 to 24)

Incidences derived from Kaplan-Meier analysis (see methods section). Participants at risk in all categories of smoking exposure: 2 years=4572; 5 years=4363; 7 years=4182; 10 years=3595; 15 years=3024.
*Number of participants at risk at each interval.
†Incidence is cumulative Kaplan-Meier survival incidence calculated over full data and evaluated at indicated times.
‡Log rank test (compared with never smokers, with no passive smoke exposure) P<0.001.
§Log rank test (compared with never smokers, with no passive smoke exposure) P=0.11.

Impact of potential mediators—waist:hip ratio and baseline insulin

Waist:hip ratio, used as a time dependent variable, was associated with increased risk of developing glucose intolerance. Each increase in the ratio by 0.01 unit was associated with an increase of 8% in risk of glucose intolerance (hazard ratio 1.08, 1.08 to 1.09). Serum insulin (hazard ratio per 1 ng/dl increase 1.04, 1.03 to 1.04) and year 7 C reactive protein (hazard ratio per 10 mg/dl increase 1.08, 1.04 to 1.12) were also associated with increased risk. When waist:hip ratio was added into the primary adjusted model above, the associations of increased incidence of glucose intolerance with current smoking (hazard ratio 1.53, 1.18 to 1.99) and passive smoke exposure among never smokers (1.28, 1.01 to 1.62) were essentially unchanged. When serum insulin and C reactive protein, and subsequently all three variables, were added, the associations were again essentially unchanged, although significance for never smokers with passive smoke exposure was borderline (hazard ratio 1.26, 0.99 to 1.61; P = 0.06).

Table 3 Association of smoking and passive tobacco smoke with incidence of glucose intolerance over 15 years of follow-up among 4572 CARDIA participants: unadjusted and adjusted hazard ratios from Cox proportional hazards analysis

	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)
Never smoker, no passive smoke exposure	Reference	Reference
Never smoker, passive smoke exposure	1.50 (1.20 to 1.88)	1.35 (1.06 to 1.71)
Previous smoker	1.26 (0.94 to 1.68)	1.17 (0.86 to 1.57)
Current smoker	1.94 (1.56 to 2.42)	1.65 (1.27 to 2.13)
Sociodemographic characteristics		
African-American (*v* white)	1.38 (1.18 to 1.60)	1.42 (1.19 to 1.69)
Male (*v* female)	2.38 (2.03 to 2.79)	1.94 (1.61 to 2.35)
Baseline age (per 10 years)	1.57 (1.25 to 1.97)	1.70 (1.34 to 2.15)
Education (at least high school *v* less than high school)	0.77 (0.66 to 0.90)	0.83 (0.69 to 1.00)
Income (per $5000)	0.96 (0.92 to 0.99)	0.99 (0.94 to 1.03)
Health behaviours		
Daily total caloric intake (per 1000 kcals)	1.06 (1.03 to 1.10)	0.99 (0.94 to 1.03)
Daily saturated fat caloric intake (per 100 kcals)	1.43 (1.17 to 1.74)	1.61 (0.79 to 3.35)
Alcohol intake (per 100 ml/day)	1.80 (1.41 to 2.30)	1.05 (0.74 to 1.49)
Physical and laboratory tests		
Triglycerides (per 1.1 mmol/l)	1.35 (1.30 to 1.40)	1.30 (1.24 to 1.37)
Systolic blood pressure (per mm Hg)	1.04 (1.03 to 1.04)	1.02 (1.01 to 1.03)
Health service related		
Has health insurance (*v* no health insurance)	0.98 (0.83 to 1.17)	1.10 (0.92 to 1.34)

*From Cox proportional hazards model adjusted for all variables in table and change in smoking (stopping or starting) during follow-up.

Discussion

In this 15 year prospective study, both current smoking and exposure to passive tobacco smoke at baseline were positively associated with increased risk of developing glucose intolerance. These effects were robust to multivariate adjustment. Use of pack years of smoking showed a consistent dose-response effect of increasing risk with increasing exposure to tobacco.

Passive exposure to smoke among never smokers conferred an intermediate risk (hazard ratio 1.35) between current smokers (hazard ratio 1.65) and never smokers with no exposure (hazard ratio 1.0, reference) for glucose intolerance, in univariate analysis. The point estimate of risk was greater among never smokers with positive passive smoke exposure than among previous smokers, both before and after multivariate adjustment. Passive smoke contains similar toxins to active smoke but is produced at different temperatures and different reducing conditions, so some toxic substances are even more concentrated in passive smoke.[21–23] If one of these concentrated toxins is related to the hypothesised pancreatic toxicity, this might explain the increased risk in passive smokers, although they have less overall exposure than current smokers.

Table 4 Stratified analysis by race and sex of 15 year Kaplan-Meier incidence and proportional hazards of glucose intolerance by tobacco exposure: CARDIA study, 1985-2001

	African-American men	African-American women	White men	White women
Current smokers				
15 year incidence of glucose intolerance (%)	29.9	19.1	30.5	9.2
Unadjusted hazard ratio (95% CI)	1.49 (0.99 to 2.24)	1.55 (1.01 to 2.38)	2.12 (1.44 to 3.13)	2.15 (1.14 to 4.07)
Adjusted hazard ratio (95% CI)	1.43 (0.88 to 2.35)	1.30 (0.79 to 2.20)	1.99 (1.25 to 3.16)	1.31 (0.63 to 2.75)
Previous smokers				
Incidence (%)	25.7	18.0	20.3	5.0
Unadjusted hazard ratio (95% CI)	1.22 (0.69 to 2.17)	1.49 (0.83 to 2.67)	1.38 (0.86 to 2.23)	1.17 (0.54 to 2.55)
Adjusted hazard ratio (95% CI)	1.26 (0.68 to 2.30)	1.38 (0.74 to 2.56)	1.15 (0.69 to 1.91)	0.91 (0.42 to 2.01)
Never smokers, passive smoke exposure				
Incidence (%)	24.4	11.8	24.3	10.0
Unadjusted hazard ratio (95% CI)	1.18 (0.78 to 1.79)	0.93 (0.59 to 1.46)	1.65 (1.11 to 2.44)	2.31 (1.22 to 4.36)
Adjusted hazard ratio (95% CI)	1.26 (0.80 to 1.97)	0.97 (0.60 to 1.56)	1.66 (1.11 to 2.49)	1.89 (0.98 to 3.64)
Never smokers, no passive smoke exposure (reference)				
Incidence (%)	20.4	12.6	14.7	4.3

Adjusted hazard ratios from separate logistic regression analyses (stratified by race and sex) and adjusted for sociodemographic factors (age, sex, race, years of education, income), as well laboratory, biological, and behavioural factors: systolic blood pressure, triglycerides, alcohol consumption, and smoking pack years collected during follow-up.

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Comparison with previous studies

Early studies evaluating an association of tobacco and risk of diabetes were negative,[8 9] but more recent studies have shown positive associations.[2–6] The fact that passive tobacco smoke exposure is an independent risk for glucose intolerance is, to our knowledge, new information. We found that people with passive exposure to tobacco smoke had an intermediate risk between current smokers and never smokers without passive smoke exposure. In fact, the risk of developing glucose intolerance for people with passive tobacco smoke exposure was similar to that of those who were previous smokers.

Our finding that the association of glucose intolerance with smoking varies across race-sex groups also adds to the previous literature. In the race and sex stratified analyses, the risks of glucose intolerance associated with tobacco exposure were greater in men than in women and greater in white people than in black people. The hazard ratio for passive smoking exposure was significant only for white men, although the decreases in sample size that accompany these stratified analyses need to be considered in the interpretation of these results.

Causal pathways

We explored potential causal pathways of tobacco exposure and incident diabetes. The main association of tobacco exposure and incidence of glucose intolerance was unchanged after introducing waist:hip ratio, baseline insulin levels, or C reactive protein into the analysis. As expected, waist:hip ratios were less favourable among smokers. However, addition of this factor to the model did not substantially attenuate the main association of smoking and glucose intolerance. This suggests that the underlying association, if causal, is not moderated by the effect of smoking on fat distribution.

We considered access to health care, socioeconomic factors, and unhealthy eating patterns as potential confounders of the association between smoking exposure and glucose intolerance. A previous study using CARDIA data has identified a strong association between tobacco exposure and lack of health insurance.[24] Smoking could thus be a marker for healthcare access variables. Although health insurance status and number of visits to the physician were not available at baseline, adjustment for these variables measured at years 5 and 7 did not change our results. Consistent with many other studies, we found that tobacco exposure was strongly associated with education and income. Of note, in another CARDIA analysis, the socioeconomic variables that we used here were sufficient to show that ethnic differences in smoking status are mostly explained by socioeconomic factors.[17] Smoking may also be marker for other unhealthy behaviours such as a high fat, high calorie diet, which may also predispose to diabetes.[25] The fact that our main associations persisted after adjustments for variables attempting to capture these socioeconomic and behavioural constructs does not rule out potential residual confounding, which is a possible limitation of our study.

Limitations

The above notwithstanding, the observational nature of our study is its major limitation, precluding definitive causal inferences. Also, the CARDIA cohort represents African-Americans and white people recruited from four urban areas in the United States. Our results are not necessarily generalisable to other ethnic minorities, rural areas, or other populations.

Conclusion

In summary, we found that tobacco exposure is associated with the development of glucose intolerance over a 15 year period, with a dose-response effect apparent. Importantly, we identified passive tobacco exposure in never smokers as a new risk factor for glucose intolerance. If confirmed by further research, these findings provide further documentation of the deleterious effects of tobacco smoking, and policy makers may use them as additional justification to reduce exposure to passive smoke.

Contributors: TKH originated the research questions, designed the study, and drafted initial and subsequent versions of the paper. SDP oversaw the analyses and reviewed and contributed to drafts. MJP reviewed and contributed to drafts and contributed content expertise. KL reviewed and contributed to drafts and contributed statistical expertise. CI reviewed and contributed to drafts. CIK reviewed and contributed to all drafts and contributed to the analytic plan. TKH and CIK are the guarantors.

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What is already known on this topic

Smoking is hypothesised to increase insulin resistance

Results of previous observational studies assessing the association of smoking and incidence of diabetes have been mixed

What this study adds

A strong association existed between both active and passive tobacco smoke exposure and subsequent development of impaired fasting glucose or diabetes over 15 years

Among smokers, total pack years smoked was associated with increasing risk of incident diabetes

The association of tobacco exposure with diabetes was greatest among white men and women

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