



Funnel plot⁴ showing asymmetry in meta-analysis of randomised controlled trials of cisapride versus placebo in non-ulcer dyspepsia. If relative risk (effect size) is plotted against 1/standard error, small negative trials should balance small positive trials. This plot indicates an absence of negative trials, which biases the pooled effect.

“privatisation” of public life has implications for society as a whole.

The production of national guidelines that are both evidence based and cost effective may pitch society against the interests of industry. For example, most of the evidence on which the 2004 NICE (National Institute for Health and Clinical Excellence) guidelines on dyspepsia are based came from randomised controlled trials funded by industry.² This created several distortions in the evidence base. Firstly, evidence from trials of proton pump inhibitors was abundant compared with data for off-patent treatments such as metoclopramide or lifestyle interventions. Secondly, placebo was chosen as a comparator when “current” treatment would have been better. Thirdly, in one instance (cisapride in non-ulcer dyspepsia) a large number of poor quality studies funded by industry led to a result that was later discounted as potentially biased (figure).³

The issues raised in the paper by Patsopoulos et al are pertinent to many areas of life, not just medicine. When she was Britain’s prime minister, Margaret Thatcher said, “There is no such thing as society.”⁵ Although we cannot ignore or shun industry, there is such a thing as civic society, and effective mechanisms

are needed to protect its interests against those of private individuals and corporations. Absolute transparency of declaration of interests is one mechanism, and investment in detailed analysis of potential bias and evidence gaps in the production of guidelines is another. Public funding for research needs to concentrate on these gaps—for example, by comparing new drugs with cheaper and older ones and complex and behavioural interventions that cannot be patented. Industry should also be more transparent over trial registration and public access to data that affect patient care. A decline in public funding for high quality research is worrying and would ultimately harm patients. However, recent funding announcements in the United Kingdom indicate that government recognises this threat, and some correction of the balance should take place in the coming decade.⁶

Competing interests: BD has been paid a speaker’s honorarium and travel expenses by Astra-Zeneca, Wyeth, Reckitt Benkiser, AxCan Pharma, and Takeda; he has also been paid for advice on research by Astra-Zeneca, Wyeth, and Merck. He has received small project grants from Astra-Zeneca and Wyeth and major grants and fellowship funding from the NHS, Medical Research Council, and National Institutes of Health (USA). He is a part time principal general practitioner and part time academic funded by Higher Education Funding Council for England. He receives travel funding from Oxford University Press as editor of *Family Practice*. He is not a member of a political party. He coauthored the technical report for the National Institute for Health and Clinical Excellence 2004 dyspepsia guideline.

- 1 Patsopoulos NA, Analatos AA, Ioannidis JPA. Origin and funding of the most frequently cited papers in medicine: database analysis. *BMJ* 2006;332:1061-3.
- 2 National Institute of Health and Clinical Excellence. *The management of dyspepsia in adult patients in primary care*. London, UK: NICE, 2004.
- 3 Soo S, Moayyedi P, Deeks J, Delaney B, Harris A, Innes M, Bennett C, Forman F. Pharmacological interventions for non-ulcer dyspepsia (full Cochrane review). In: *The Cochrane Library*. Oxford: Update Software, 2001; issue 3.
- 4 Sterne JAC, Egger M, Smith GD. Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101-5.
- 5 Douglas K. *Margaret Thatcher interviewed in “Woman’s Own”*, 23 Sep 1987. www.margarethatcher.org/speeches/displaydocument.asp?docid=106689 (accessed 9 Feb 2006).
- 6 Department of Health. *Best research for best health*. London: DOH, 2006. www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4127127&chk=uSh6qN (accessed 9 Feb 2006).

(Accepted 20 February 2006)
doi 10.1136/bmj.38771.471563.80

Editorial by Panagiotakos and Pitsavos

Deep South Center on Effectiveness Research, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA

Thomas K Houston assistant professor of medicine
Catarina I Kiefe professor of medicine
continued over

BMJ 2006;332:1064-7

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

Thomas K Houston, Sharina D Person, Mark J Pletcher, Kiang Liu, Carlos Iribarren, Catarina I Kiefe

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.

This is the abridged version of an article that was posted on bmj.com on 7 April 2006: <http://bmj.com/cgi/doi/10.1136/bmj.38779.584028.55>

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 \geq 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

The evidence that smoking is an independent risk factor for the development of diabetes is still considered preliminary.¹ Some studies have shown a dose-response association between smoking and incidence of diabetes,^{2,3} but others have not.⁴ 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 and is related to a more unhealthy distribution of upper body weight and greater waist:hip ratio.⁵⁻⁷ Smoking has also been associated with risk of chronic pancreatitis and pancreatic cancer, suggesting that tobacco smoke may be directly toxic to the pancreas.⁸

Previous studies have used only self report, were not validated by biological measures, and have not considered passive (secondhand) exposure to tobacco. Also, previous studies have not included high proportions of African-Americans, a population at particular risk of developing diabetes.⁹ We used a population based longitudinal study of African-American and white young adults to evaluate the association of smoking and passive tobacco smoke exposure with risk of incident glucose intolerance and to explore potential causes of 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 development of cardiovascular risk from young adulthood to midlife. In 1985-6, 5115 black and white men and women aged 18-30 years were randomly selected from census tracts and healthcare plan membership in Birmingham, Chicago, Minneapolis, and Oakland, USA. Participants were examined 2, 5, 7, 10, and 15 years after baseline. After exclusions and attrition, 4657 participants with at least one follow-up examination remained in the dataset.

Definition of baseline tobacco exposure (main independent variable)—After excluding 85 participants who reported passive smoke but had cotinine concentrations over 15 mg/ml, we divided the remaining 4572 participants into four categories of tobacco exposure by using a combination of self report and serum cotinine measures at baseline: current smokers, previous smokers, never smokers with exposure to passive smoke, and never smokers without reported passive smoke exposure.

Definition of outcomes—The main outcome was time to development of glucose intolerance, defined as American Diabetes Association guideline defined impaired fasting glucose or diabetes, or report of being prescribed antidiabetic drugs, at years 2, 5, 7, 10, or 15.

Covariates and potential mediating variables—Baseline covariates included self reported ethnicity, age, sex, years of education, mean daily ethanol intake, total calorie intake and physical activity. Covariates collected at baseline and follow-up included number of pack years smoked, systolic blood pressure, hip and waist circumference, serum insulin, household income, having health insurance, and number of physician visits. 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 available at year 7. We assessed the impact of these variables after adjusting for potential confounding covariates.

Data analysis

The major independent variable was tobacco exposure at baseline. We made individual comparisons for differences in covariates for each category of tobacco exposure. We assessed the association of tobacco exposure with 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). We assessed whether current smoking, previous smoking, and passive exposure to tobacco smoke were related to a greater risk of development of glucose intolerance and diabetes or incidence at baseline.

We developed multivariate models to adjust the association between levels of smoke exposure and incidence of glucose intolerance for various potential confounders. The final primary model included all covariates that were found to differ significantly by tobacco exposure and was further adjusted for time dependent change in smoking (stopping or starting). We repeated these analyses with diabetes as the outcome. We then introduced potential mediating factors (baseline waist:hip ratio and insulin concentration, year 7 C reactive protein) to evaluate for further attenuation of the main effect.

University of California, San Francisco, CA, USA

Mark J Pletcher
assistant professor of medicine

Northwestern University, Evanston, IL, USA

Kiang Liu
professor of medicine

Kaiser Permanente, Oakland, CA

Carlos Iribarren
research scientist

University of Alabama at Birmingham, Birmingham, AL

Thomas K Houston
assistant professor of medicine

Sharina D Person
associate professor of medicine

Catarina I Kiefe
professor of medicine

Correspondence to: T K Houston, Division of General Internal Medicine, University of Alabama at Birmingham, 510 20th Street South, FOT 720, Birmingham, AL 35294, USA
thouston@uabmc.edu

Table 1 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 *bmj.com*). 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.

Results

Among the 4572 participants, we identified 1386 current smokers at baseline, 621 previous smokers, 1452 never smokers with passive tobacco smoke exposure, and 1113 never smokers with no passive tobacco smoke exposure. 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. Mean age of participants was 25 (SD 3.6) years, 2529 (55%) were women, and 2283 (50%) were African-American.

Incidence of glucose intolerance and smoking or tobacco smoke exposure

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 incidence of diabetes was 3.1% (2.6% to 3.7%). Fifteen year incidence of glucose intolerance was greatest among current smokers and lowest among never smokers with no exposure to passive smoke (table 1). 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 model, current smokers had a higher risk of glucose intolerance than never smokers with no passive smoke exposure, after adjustment for baseline sociodemographic, biological, and behavioural factors (table 2). 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 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 these results.

Pack years as a marker for amount of tobacco exposure

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

The association between current smoking and glucose intolerance was stronger in white people than in black people for both women and men (*P*<0.001 for overall interaction with race-sex) (see *bmj.com*).

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

Waist:hip ratio 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 each of the three variables was added into the primary adjusted model the associations between incidence of glucose intolerance and current smoking and passive smoke exposure among never smokers were unchanged (see *bmj.com*).

Table 2 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 kcal)	1.06 (1.03 to 1.10)	0.99 (0.94 to 1.03)
Daily saturated fat caloric intake (per 100 kcal)	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. 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 between current smokers and never smokers with no exposure for glucose intolerance. The point estimate of risk was greater among never smokers with positive passive smoke exposure than among previous smokers. Some toxic substances are even more concentrated in passive smoke.¹⁰⁻¹² 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.

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, adding 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, socio-economic factors, and unhealthy eating patterns as potential confounders of the association between smoking exposure and glucose intolerance. Adjustment for health insurance status and number of visits to the physician 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. Smoking may be a marker for other unhealthy behaviours such as a high fat, high calorie diet, which may predispose to diabetes.¹³ The fact that our main associations persisted after adjustments for variables attempting to capture socio-economic and behavioural constructs does not rule out potential residual confounding, which is a possible limitation of our study.

Limitations

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 urban areas in the United States. Our results are not necessarily generalisable to other ethnic minorities, rural areas, or other populations.

Conclusion

We found that tobacco exposure is associated with the development of glucose intolerance over a 15 year

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

period, with a dose-response effect apparent. Importantly, we identified passive tobacco exposure in never smokers as a new risk factor for glucose intolerance.

Contributors: See bmj.com.

Funding: Work on this manuscript was supported (or partially supported) by contracts to the University of Alabama at Birmingham, Coordinating Center, N01-HC-95095; University of Alabama at Birmingham, Field Center, N01-HC-48047; University of Minnesota, Field Center, N01-HC-48048; Northwestern University, Field Center, N01-HC-48049; Kaiser Foundation Research Institute, N01-HC-48050; University of California, Irvine, Echocardiography Reading Center, N01-HC-45134; and Harbor-UCLA Research Education Institute, Computed Tomography Reading Center, N01-HC-05187 from the National Heart, Lung and Blood Institute.

Competing interests: None declared.

- Haire-Joshu D, Glasgow RE, Tibbs TL. Smoking and diabetes. *Diabetes Care* 1999;22:1887-98.
- Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, et al. Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 1993;83:211-4.
- Kawakami N, Takatsuka N, Shimizu H, Ishibashi H. Effects of smoking on the incidence of non-insulin-dependent diabetes mellitus: replication and extension in a Japanese cohort of male employees. *Am J Epidemiol* 1997;145:103-9.
- Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care* 2001;24:1590-5.
- Janzon L, Berntorp K, Hanson M, Lindell SE, Trelle E. Glucose tolerance and smoking: a population study of oral and intravenous glucose tolerance tests in middle-aged men. *Diabetologia* 1983;25:86-8.
- Atvall S, Fowelin J, Lager I, Von Schenck H, Smith U. Smoking induces insulin resistance—a potential link with the insulin resistance syndrome. *J Intern Med* 1993;233:327-32.
- Shimokata H, Muller DC, Andres R. Studies in the distribution of body fat. III. Effects of cigarette smoking. *JAMA* 1989;261:1169-73.
- Talamini G, Bassi C, Falconi M, Sartori N, Salvia R, Rigo L, et al. Alcohol and smoking as risk factors in chronic pancreatitis and pancreatic cancer. *Dig Dis Sci* 1999;44:1303-11.
- Carter JS, Pugh JA, Monterrosa A. Non-insulin-dependent diabetes mellitus in minorities in the United States. *Ann Intern Med* 1996;125:221-32.
- Chan-Yeung M, Dimich-Ward H. Respiratory health effects of exposure to environmental tobacco smoke. *Respirology* 2003;8:131-9.
- United States Environmental Protection Agency. *Respiratory health effects of passive smoking: lung cancer and other disorders*. Washington, DC: US EPA, 1992;3.2-2.10.
- National Cancer Institute. Health effects of exposure to environmental tobacco smoke: the report of the California Environmental Protection Agency. Bethesda, MD: National Institutes of Health, National Cancer Institute, US Department of Health and Human Services, 1999:12-3.
- Van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Ann Intern Med* 2002;136:201-9.

(Accepted 23 February 2006)

doi 10.1136/bmj.38779.584028.55