Cigarette Smoking Is Not Associated With Hyperinsulinemia: Evidence Against a Causal Relationship Between Smoking and Insulin Resistance

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Previous reports of a relationship between cigarette smoking and hyperinsulinemia and insulin resistance provide an important possible mechanism by which smoking could be associated with the metabolic cardiovascular syndrome and hence with ischemic heart disease. However, few previous studies have been able to adjust for all the possible confounding factors related both to smoking and to insulin resistance. Therefore, we examined this association in a population-based cohort study of 1,122 individuals aged 40 to 65 years who underwent a 75-g oral glucose tolerance test with specific measurement of insulin, 32,33-split proinsulin, and intact proinsulin concentrations. Physical activity was quantified using the Paffenbarger questionnaire, and smoking status and alcohol consumption were determined using the Health and Lifestyle Survey questionnaire; 17.4% of the population were current smokers and 32.4% were ex-smokers. Current smoking was associated with reduced overall obesity as indicated by the body mass index (BMI) but an increase in central adiposity as measured by the waist to hip ratio (WHR). There were also significant associations between cigarette smoking and the pattern of alcohol intake and physical inactivity. In unadjusted analyses, current smoking was associated with lower fasting and 120-minute insulin and also 120-minute glucose compared with levels in nonsmokers. Adjustment for confounding by age and BMI reduced these differences, but they were increased by adjustment for central obesity. We conclude from this study that a causal relationship between cigarette smoking and insulin resistance is unlikely.

THE OBSERVATION that insulin resistance is associated with a cluster of other metabolic abnormalities (low high-density lipoprotein [HDL] cholesterol, elevated triglycerides, glucose intolerance, and hypertension) has led to the suggestion that this metabolic cardiovascular syndrome could provide a causal pathway linking insulin resistance with ischemic heart disease.[1] Although the determinants of insulin resistance remain uncertain, it is likely that both genetic and environmental factors are important. Since cigarette smoking is a major risk factor for ischemic heart disease,[2] some investigators have questioned whether any of the effect of smoking on cardiovascular risk could be mediated through an association with insulin resistance.[3-7] Such a suggestion is backed by the observation that in some studies cigarette smoking is an independent risk factor for non–insulin-dependent diabetes mellitus (NIDDM),[8-10] a condition partly determined by impaired insulin sensitivity.[11,12]

The evidence for an association between cigarette smoking and insulin resistance comes from a variety of different studies. These can be broadly divided into physiological studies in which a precise measure of insulin resistance is made and subjects are matched for important confounding variables,[3,4,7,13] and epidemiological studies in which proxy indicators of insulin resistance are measured and adjustment for confounding is made in the analyses.[14-16] However, in many of these studies, an incomplete list of possible confounding variables has been assessed. Cigarette smoking has a complex relationship with central and regional adiposity,[17,18] both of which have important associations with insulin resistance. Cigarette smoking is also associated with different patterns of alcohol intake and physical inactivity. Since these behaviors may have important effects on insulin resistance,[19,20] they need to be adequately considered in any analysis.

The aim of this investigation was to describe the relationship between cigarette smoking and fasting and postload insulin levels in a population-based study of adult men and women, and to examine the extent to which the relationship could be explained by the observed anthropometric and behavioral differences between smokers and nonsmokers. The use in this study of specific insulin measurement removes the possibility of measurement error due to the cross-reactivity of the nonspecific insulin assays that have been used in many previous studies.[21]

SUBJECTS AND METHODS

The Isle of Ely Study is a longitudinal cohort study of the etiology and pathogenesis of NIDDM and related metabolic disorders.[22] A sample of 1,122 subjects were selected at random from a sampling frame consisting of all adults free of known diabetes who were registered with the single general medical practice in the City of Ely (response rate, 74%). No data are available on members of the eligible population who did not participate. Volunteers attended for a standard 75-g oral glucose tolerance test and a clinical examination that included a dietary and medical questionnaire and anthropometric measurements. In keeping with World Health Organization (WHO) recommendations,[23] volunteers were asked to fast from 10:00 PM the previous evening and to abstain from smoking, use of a nicotine patch, or chewing nicotine gum on the morning of the test. Smoking status and alcohol intake were assessed using the Health and Lifestyle Survey questionnaire.[24] Leisure time physical activity was assessed using the Paffenbarger questionnaire[25,26] with standard coding of specific activities using published energy costs for recreation and sports.[27] Serum and plasma samples were obtained at fasting and 30 and 120 minutes after the glucose load and were immediately separated in a cooled centrifuge at 4°C. They were placed on ice and stored at −70°C

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within 4 hours. Plasma glucose level was measured by a hexokinase method.[28] Plasma insulin was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels.[29,30] Insulin concentrations were measured in baseline, 30-minute, and 120-minute samples. Plasma intact proinsulin and 32,33-split proinsulin levels were measured on fasting samples using immunoradiometric assays.[29] The study was approved by the Cambridge Local Research Ethics Committee.

Statistical Methods

WHO criteria for diabetes and impaired glucose tolerance were used to classify subjects.[23] Since the underlying distributions of all the insulin variables were skewed, geometric means (with 95% confidence intervals) were calculated rather than arithmetic means. Comparisons between smoking categories were made with ANOVA. The effects of the various confounding factors on the relationship between smoking and fasting insulin concentration were assessed in a series of multiple regression models by observing changes in the regression coefficients for a pair of dummy variables comparing nonsmokers with ex-smokers and current smokers. In this way, both the direction and magnitude of confounding were assessed.

RESULTS

As previously reported,[22] 51 subjects were found to have newly diagnosed NIDDM by WHO criteria, 188 had impaired glucose tolerance, and 883 had normal glucose tolerance. All further analyses were conducted in the nondiabetic population (n = 1,071). A full smoking history was available on all these subjects. Thirty-six cigar or pipe smokers were excluded from further analyses because they constitute a group too small for meaningful separate analysis. The prevalence of current smoking in this population was 17.4%, and 32.4% of the population were ex-smokers. Table 1 shows the characteristics of the population by gender and smoking category with a comparison between groups by ANOVA. In both men and women, there were differences in the age of the smoking groups, with ex-smokers being older than either current smokers or nonsmokers. Female current smokers had a lower body mass index (BMI) ($P = .02$ for t test comparison of means) but a higher waist to hip ratio (WHR) ($P = .001$) than nonsmokers. In men, there was no significant difference in BMI between current smokers and nonsmokers, but current smokers had a significantly elevated WHR ($P = .004$). In both genders, the mean BMI in ex-smokers was significantly higher than in current smokers ($P = .01$ in men and $P = .025$ in women).

Table 1. Subject Characteristics by Smoking Category and Gender

Characteristic	Nonsmokers	Ex-smokers	Current Smokers	Significance of F Test
No. of subjects				
M	155 (35.9%)	192 (44.4%)	85 (19.7%)	
F	365 (60.5%)	143 (23.7%)	95 (15.8%)	
Age (yr)				
M	52.8 ± 7.7	55.4 ± 8.0	53.2 ± 7.1	.005
F	53.1 ± 7.6	54.8 ± 7.5	52.3 ± 7.7	.02
BMI ($kg \cdot m^{-2}$)				
M	25.5 ± 3.0	26.5 ± 3.0	25.5 ± 3.3	.003
F	25.9 ± 4.8	26.1 ± 5.5	24.6 ± 4.2	.047
WHR*				
M	0.89 ± 0.06	0.91 ± 0.06	0.91 ± 0.06	<.0001
F	0.76 ± 0.05	0.76 ± 0.06	0.78 ± 0.05	.02

NOTE. Comparison between groups was made by ANOVA; 36 cigar or pipe smokers are excluded from this analysis.

Abbreviations: M, male; F, female.

*Mean ± SD.

Table 2. Categories of Alcohol Intake by Smoking Category and Gender

Alcohol Intake (U/wk)	Nonsmokers		Ex-smokers		Current Smokers	
	No.	%	No.	%	No.	%
Men						
None	33	21.2	28	14.6	20	23.5
0-5	70	45.2	69	35.9	24	28.2
5-10	25	16.1	39	20.3	9	10.6
>10	27	17.4	56	29.2	32	37.6
Total	155		192		85	
$\chi^2 = 20.5, P = .002, df = 6$						
Women						
None	149	40.1	38	26.6	27	28.4
0-5	173	47.4	65	45.5	42	44.2
5-10	25	6.8	27	18.9	14	14.7
>10	18	4.9	13	9.1	12	12.6
Total	365		143		95	
$\chi^2 = 30.0, P = .0001, df = 6$						

Table 2 shows that there was a significant association in both men and women between smoking status and alcohol intake, quantified in units of alcohol per week. In men, the major difference was that more smokers and ex-smokers drank in excess of 10 U/wk compared with those who had never smoked. Fewer female ex-smokers or current smokers were nondrinkers compared with the never-smokers. The smoking categories also differed in the amount of leisure time physical activity reported. A comparison between smoking categories was made for the total number of metabolic equivalents (METS) per week using the Kruskal-Wallis one-way ANOVA. In women, there was an overall difference ($P = .014$), with smokers being less physically active. In men, there were no significant group differences. Since the ex-smokers are theoretically a heterogeneous group, a comparison was made between the anthropometric and metabolic characteristics of this group stratified by time since quitting smoking (<10 years v ≥10 years). No significant differences were found in mean fasting insulin concentration or any of the lipid variables. In male ex-smokers, the WHR (mean ± SD) in those who stopped smoking less than 10 years ago was 0.94 ± 0.06 compared with 0.91 ± 0.05 in those who quit at least 10 years earlier ($P = .005$).

Table 3 shows the unadjusted data for insulin and glucose concentrations at each time point during the oral glucose tolerance test, and also the fasting intact and partially split proinsulin concentrations. Fasting insulin concentrations were reduced in current smokers in comparison to nonsmokers and ex-smokers of both genders, although ANOVA suggested that these differences did not reach significance in men. Although there were no significant differences in fasting plasma glucose concentrations, there were group

Table 3. Plasma Insulin and Glucose Concentrations by Smoking Category and Gender

Insulin/Glucose	Nonsmokers	Ex-smokers	Current Smokers	*P*
Men				
No.	155	192	85	
Insulin (pmol · L^{-1})				
Fasting	41.0 (37.1-45.3)	42.6 (39.6-45.8)	36.2 (32.1-40.9)	NS
30 min	256 (230-284)	278 (254-304)	261 (230-297)	NS
120 min	229 (207-253)	240 (223-258)	174 (154-196)	<.01
Split proinsulin	5.1 (4.8-5.5)	5.6 (5.0-6.3)	5.1 (4.5-5.8)	NS
Intact proinsulin	3.4 (3.3-3.6)	3.5 (3.2-3.8)	3.3 (2.9-3.6)	NS
Glucose (mmol · L^{-1})				
Fasting	5.84 ± 0.54	5.91 ± 0.57	5.85 ± 0.57	NS
30 min	8.60 ± 1.57	8.87 ± 1.60	8.84 ± 1.71	NS
120 min	6.25 ± 1.48	6.46 ± 1.66	5.75 ± 1.60	<.01
Women				
No.	365	143	95	
Insulin				
Fasting	40.0 (37.8-42.3)	42.0 (38.3-46.2)	35.1 (31.5-39.1)	.04
30 min	262 (248-277)	291 (267-317)	256 (228-288)	NS
120 min	241 (227-256)	266 (241-294)	205 (179-235)	<.01
Split proinsulin	5.1 (4.8-5.5)	5.6 (5.0-6.3)	5.1 (4.5-5.8)	NS
Intact proinsulin	3.4 (3.3-3.6)	3.5 (3.2-3.8)	3.3 (2.9-3.6)	NS
Glucose				
Fasting	5.66 ± 0.59	5.65 ± 0.56	5.56 ± 0.55	NS
30 min	8.08 ± 1.57	8.16 ± 1.60	7.90 ± 1.55	NS
120 min	6.46 ± 1.56	6.43 ± 1.59	5.64 ± 1.50	<.01

NOTE. Results are the mean ± SD for glucose measurements and the geometric mean (95% confidence interval) for all insulin measurements. Comparison between groups was made by ANOVA.

Abbreviation: NS, nonsignificant.

differences in the 2-hour glucose level, with the mean being significantly reduced in current smokers in men and women.

Table 4 shows the mean insulin and glucose concentrations by category of alcohol intake with significance values for heterogeneity and linear trend. The data show that the 120-minute glucose concentration was negatively associated with alcohol intake, but the effect was much stronger in women. Fasting insulin decreased with increasing alcohol intake in men, but in women a U-shaped relationship was demonstrated, with the lowest mean insulin concentration in women who drank 5 to 10 alcohol U/wk. Table 5 shows the geometric mean insulin concentration by gender and category of leisure time physical activity. Inactive subjects were those who reported no leisure time physical activity (39% of men and 43% of women). The moderately active group undertook between 1 and 15 MET h/wk, and the active group took more than 15 MET h/wk of physical activity. In both genders, there is a significant negative association between increasing physical activity category and fasting insulin.

As there were significant univariate associations between cigarette smoking, alcohol intake, physical inactivity, and obesity, we undertook sex-specific multiple regression analyses with log-transformed fasting insulin as the dependent variable (Table 6). Smoking category was entered as a pair of binary indicator or dummy variables. Possible confounding factors were added in turn to the model to demonstrate the effects on the regression coefficients. In the initial model, there was no significant difference in fasting insulin

Table 4. Plasma Insulin and Glucose Concentrations by Category of Alcohol Intake and Gender

Insulin/ Glucose	Alcohol Units per Week				*P* for Heterogeneity	*P* for Linear Trend
	None	0-5	5-10	>10		
Men						
No.	85	176	78	124		
Insulin						
0 min	42.9	40.8	40.7	38.0	NS	NS
30 min	268	249	274	267	NS	NS
120 min	228	233	215	199	NS	NS
Glucose						
0 min	5.84	5.87	5.84	5.91	NS	NS
30 min	8.62	8.79	8.69	8.73	NS	NS
120 min	6.36	6.30	6.19	6.04	NS	NS
Women						
No.	216	279	68	43		
Insulin						
0 min	42.1	39.0	34.5	41.2	NS	NS
30 min	266	269	266	264	NS	NS
120 min	249	247	216	207	NS	.04
Glucose						
0 min	5.73	5.58	5.60	5.69	.02	NS
30 min	8.39	7.93	7.91	7.72	.002	<.001
120 min	6.69	6.23	5.98	5.82	<.001	<.001

NOTE. Results show the arithmetic mean for glucose measurements in mmol · L^{-1} and the geometric mean for all insulin measurements in pmol · L^{-1}. Measures of the spread of the data have not been included for reasons of clarity. Comparison between groups for heterogeneity was made by ANOVA. A *P* value for linear trend is also included.

Abbreviation: NS, nonsignificant.

Table 5. Geometric Mean (pmol/L) Fasting Insulin Concentration (95% confidence interval) by Physical Activity Category and Gender

Physical Activity	Men	Women
Inactive	44.8 (40.7-49.3)	43.4 (40.1-46.9)
Moderately active	39.2 (35.7-43.1)	37.9 (35.0-41.2)
Active	38.7 (34.4-43.6)	35.5 (32.2-39.3)
P for linear trend	.04	.001

between nonsmokers and ex-smokers, and no true difference was unmasked in the subsequent models that include the potential confounders. In the model without confounders, current smoking was associated with a significant reduction in fasting insulin in women. In men, the reduction as judged by the regression coefficient was of a similar magnitude but not statistically significant. Adjustment for age by itself made little difference, but the addition of BMI approximately halved the effect of current smoking in women. This change was predictable, since the mean BMI in women who smoke was lower than in nonsmokers. Addition of the WHR to the model markedly increased the negative association between smoking and fasting insulin. In this model, both BMI and WHR predicted fasting insulin, suggesting there is some degree of independence between these factors. We also examined the relationship between fasting insulin, BMI, and WHR stratified by smoking status to check for interaction. There was no evidence that the relationship between fasting insulin and BMI and WHR was affected by smoking category (data not shown).

In the model that included all possible confounding variables, the association of smoking with fasting insulin was still negative, but the effect was diminished. Alcohol was initially entered into the model as a continuous variable. A separate analysis was undertaken with alcohol entered as a nonordered categorical variable to examine the possibility of a nonlinear relationship between alcohol intake and fasting insulin. No independent association with alcohol intake was demonstrated. Finally, physical activity was added to the model, with no effect. Taken together, these data suggest that cigarette smoking has an association with lower fasting insulin and that the size of the effect is affected by which confounding factors are considered.

DISCUSSION

We found no association between cigarette smoking and hyperinsulinemia, either before or after adjustment for possible confounding variables. Indeed, cigarette smoking was associated with lower fasting insulin and 2-hour plasma glucose concentrations. These observations lead us to conclude that a causal relationship between cigarette smoking and insulin resistance is unlikely. However, this inference is dependent on the assumption that fasting insulin concentration is a proxy measure for insulin resistance. This assumption has been shown to be valid in a number of studies in which a comparison was made to more physiological assessments of insulin resistance.[31,32] However, there is a necessary trade-off between the feasible size of a study and the precision of measurement of the variable of interest. In smaller studies, a more precise assessment of insulin resistance is possible, but there is much greater potential for selection bias and confounding. Although attempts are made to reduce the latter by matching, this has to be carefully undertaken to eliminate the potential for confounding. In larger epidemiological studies like our own, selection bias is eliminated provided the study is population-based and has a sufficient response rate. The adjustment for confounding is undertaken in the analysis rather than by restriction, and therefore its effects can be more easily observed and quantified. The problem with this form of study is that one must rely on a proxy measure of insulin resistance. However, if the size of the study is sufficient, it is reasonable to use a proxy measure provided it does not introduce any differential bias.

The published evidence of an association between smoking and insulin resistance is inconsistent.[3,4,7,13-16,33,34] Some of the variation between studies can be attributed to study design and the extent to which confounding is removed. In our study, as in others,[17,18] the effect of smoking is to reduce overall obesity but accentuate its central deposition. The multiple regression analyses in Table 6 show that adjustment for age and obesity alone tends to reduce differences between smokers and nonsmokers, whereas introduction of the WHR as a separate confounding variable accentuates the true group differences. Therefore, studies that either match or adjust for age and BMI alone would tend to find a smaller negative association between smoking and fasting insulin or possibly a small positive one. In small studies such

Table 6. Results of Six Multiple Regression Models With Log-Transformed Fasting Insulin as the Dependent Variable, Showing the Effect of Inclusion of Different Confounding Factors

	Confounding Variables Included in Model					
Group	None	Age	Age, BMI	Age, BMI, WHR	Age, BMI, WHR, Alcohol	Age, BMI, WHR, Alcohol, Physical Activity
Men						
Ex-smokers	.038	.039	−.031	−.053	−.036	−.002
Current smokers	−.125	−.124	−.122	−.169*	−.111*	−.101
Women						
Ex-smokers	.049	.055	.044	.044	.040	.010
Current smokers	−.139*	−.135*	−.065	−.107*	−.070	−.090

NOTE. The results show regression coefficients for the dummy variables coding for ex-smokers and current smokers compared with nonsmokers.
*$P < .05$.

as the one reported by Facchini et al,[3] removal of confounding due to central adiposity is claimed because there is no significant difference in the mean WHR between a group of 20 smokers and 20 nonsmokers. However, given the size of the difference in WHR demonstrated in our study (Table 1), a type II error cannot be excluded. Thus, undue confidence can be expressed about the removal of confounding with this sort of group-matching for a variable that has a large effect but for which differences are small.

A number of other possibilities could explain the variation in the associations described in different studies.[3,4,7,13-16,33,34] Firstly, there could be real differences between populations. Because of the important effect in these analyses of differences between smoking groups with respect to the overall degree of obesity, its site of deposition, and associations with other lifestyle behaviors, any differences in the pattern of these associations could have an important impact on the unadjusted and adjusted effect of smoking on fasting insulin. Variation in the relationship between smoking and insulin resistance was demonstrated in the European Fat Distribution Study.[35] The cohort of Italian men in whom smoking was particularly prevalent had the lowest fasting insulin of the groups studied. Whether this is attributable to differences in the pattern of association of smoking with possible confounding variables remains uncertain.

The use of nonspecific assays to measure insulin levels is a theoretical source of measurement error,[21] since the metabolic precursor molecules proinsulin and 32, 33-split proinsulin that cross-react with nonspecific insulin assays are disproportionately elevated in individuals with glucose intolerance.[36,37] However, we have shown in the Isle of Ely Diabetes Project that the magnitude of such an effect is relatively small and does not reverse the finding of hyperinsulinemia in individuals with NIDDM or impaired glucose tolerance.[38] The last form of possible bias is due to selective publication of results of studies that demonstrate positive associations. This becomes more likely when the positive association is biologically plausible and when the exposure of interest is already considered harmful.

If smoking had a strong association with insulin resistance, one would perhaps expect all the features of the metabolic cardiovascular syndrome to be associated with smoking. The evidence for this is patchy. Cigarette smoking has been shown in a previous report from our laboratory[39] and in many other studies to be associated with the dyslipidemic profile that is characteristic of the metabolic cardiovascular syndrome, ie, decreased HDL and elevated triglyceride.[40] However, there is little evidence of an association of chronic smoking with increased blood pressure. Although a number of studies suggest that smoking acutely increases blood pressure,[41,42] a recent review of the evidence for an association between chronic cigarette smoking and blood pressure found an inverse relationship in 11 of 14 studies reviewed.[43] In the Ely study, subjects were asked not to smoke on the morning of the test, in accordance with WHO recommendations for conducting an oral glucose tolerance test, and so it is likely that only the chronic effects of smoking are observed. By analogy with the effect on blood pressure, it is possible that the acute and chronic effects of smoking on insulin resistance could be different. If so, then variations between studies in the extent to which subjects were asked to abstain from smoking could account for the apparent diversity of study results.

Finally, since insulin resistance is a major determinant of future risk for NIDDM,[11,12] then factors causally associated with insulin resistance should be strong predictors of the development of NIDDM. Although there are a number of studies that suggest the risk of NIDDM is elevated among smokers,[8-10,44] they do not always adjust for all possible confounding variables, and there are a number of studies in which this association is not demonstrated.[45,46]

Thus, the negative finding in this study and the inconsistency of the reported associations in other studies, together with the absence of a simple relationship between smoking and the other features of the insulin resistance syndrome, strongly suggest there is no causal relationship between smoking and insulin resistance. The complex relationships between smoking and other behaviors (alcohol intake and physical activity), obesity, hyperinsulinemia, and the dyslipidemia and hypertensive features of the metabolic cardiovascular syndrome provide an important lesson for future studies of the etiology of this syndrome. They suggest that researchers should plan the design of their studies on the assumption that the analyses will have to be undertaken stratified by smoking status.

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