



Published in final edited form as:

Ann Epidemiol. 2009 June ; 19(6): 365–371. doi:10.1016/j.annepidem.2009.01.013.

CIGARETTE SMOKING IS ASSOCIATED WITH CONVERSION FROM NORMOGLYCEMIA TO IMPAIRED FASTING GLUCOSE: THE WESTERN NEW YORK HEALTH STUDY

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Abstract

Purpose—To determine whether cigarette smoking is associated with the conversion from normoglycemia to impaired fasting glucose (IFG).

Methods—During 2003–2004 1,455 participants (mean age 56.5, range 35–79) from the Western New York Health Study who were free of Type 2 diabetes and known cardiovascular disease at baseline (1996–2001) were reexamined (68% response rate). Incident IFG was defined as a subject whose baseline fasting plasma glucose was <100 mg/dl (normoglycemic) and between 100 and 125 mg/dl at follow-up. Prevalent IFG (n=528) was excluded. Baseline smoking status was categorized as never, former or current.

Results—Of the 1,455 participants, 924 were normoglycemic at baseline: 101/924 converted to IFG over six- years. Compared to those who remained normoglycemic, converters to IFG were at baseline older, had a larger BMI, more likely to be hypertensive, currently smoke, and have a family history of T2DM (all $P < 0.05$). Multivariate logistic regression demonstrated that compared to subjects who remained normoglycemic, the OR of incident IFG among former and current smokers (vs. never) was 1.68 (95% confidence interval: 0.99, 2.80) and 2.35 (95% confidence interval: 1.17, 4.72) ($P_{\text{trend}} = 0.008$), respectively.

Conclusion—Smoking was positively associated with incident IFG after accounting for several putative risk factors.

Keywords

cigarette smoking; impaired fasting glucose; epidemiology; risk factors

Type 2 diabetes mellitus (T2DM) is a formidable public health problem leading to premature morbidity and mortality and contributing to increased health care costs. Putative risk factors associated with the development of T2DM are age, ethnicity, obesity, family history of T2DM, and physical inactivity. Moreover, both the Diabetes Prevention Program and the Finish

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Diabetes Prevention Study have shown the strong predictive nature of impaired fasting glucose (IFG) on diabetes risk (1,2).

Like the growing epidemic of T2DM, the number of individuals with pre-diabetes (defined as impaired fasting glucose (fasting plasma glucose ≥ 100 mg/dl and < 126 mg/dl) or impaired glucose tolerance (plasma glucose ≥ 140 and < 200 mg/dl after an oral glucose tolerance test) is also on the rise. In 2007 approximately 57 million Americans had pre-diabetes (3). The pre-diabetic period provides a prime opportunity to prevent or delay not only T2DM, but to possibly reduce the microvascular and/or macrovascular complications as well. Therefore, identification of impaired fasting glucose and its modifiable risk factors would offer the chance to intervene at an earlier point in the natural history of disease.

Cigarette smoking may be a common antecedent of both IFG and diabetes. Epidemiologic evidence accumulated over the last few decades convincingly establishes smoking as a risk factor for T2DM with a relative risk (RR) ranging from 1.5 to nearly 6.0 (4–18). There is, however, a paucity of information on the association between smoking and impaired fasting glucose. Two studies among occupational cohorts of Japanese men presented contradictory results: one prospective study reported a RR of 2.56 (95% confidence interval: 1.32, 4.95) (19) whereas a cross-sectional study found no association (20). A third study, a population-based cross-sectional study of Swedish men found a null association between smoking and impaired glucose tolerance (IGT), but did not examine smoking and IFG (12).

The Western New York Follow-up Study was designed to examine the incidence of type 2 diabetes and, therefore provides a unique opportunity to prospectively examine whether smoking behavior at baseline (never, former, or current) is associated with the conversion from normoglycemia (NGT) to impaired fasting glucose in a community-based cohort that includes both men and women from Western New York

MATERIALS AND METHODS

The study design and methodology of the original Western New York Health Study have been previously published (21–23). From 1996–2001 participants were enrolled as healthy control subjects in the Western New York Health Study, a series of case-control studies of alcohol drinking patterns and risk of cardiovascular disease (CVD) and lung cancer in Erie and Niagara Counties, New York. The initial cohort of control participants was randomly selected from drivers' license lists for those under age 65, and from the Health Care Finance Administration rolls for persons aged 65 years and older (response rate 59.5%). During 2003–2004 we conducted the first follow-up. Eligible participants for this follow-up study were at the baseline examination 35–79 years old (mean age 56.5) and without known clinical cardiovascular disease (self-reported MI, angina or revascularization surgery) or Type 2 diabetes mellitus (measured fasting plasma glucose > 125 mg/dl or self report of a physician diagnosis and taking medication) (n=2,652). Exclusion criteria were self-report of all cancers except skin cancer, and Type 1 diabetes, as well as physical or mental impairment that would prohibit the subject from completing all parts of the protocol (n=165); permanent change in residence to out-of-state (n=39), deceased (n=67), or inability to contact and determine eligibility (n=242). This left 2,139 persons eligible for the follow-up examination: 1,455 completed the full clinic protocol (68% response rate). At baseline 927 of the 1455 subjects were normoglycemic, the other 528 had prevalent IFG and therefore were not considered in this analysis. Because of missing baseline data on smoking status for three subjects the final analytic data set consisted of 924 normoglycemic subjects at baseline, 101 of who converted to IFG over the six-year follow-up.

At baseline, compared to persons who refused, participants were less likely to smoke and more likely to have completed high school. There were no significant differences in fasting glucose concentrations, BMI or sex ratio (data not presented). The mean follow-up time was 5.9 years (SD = 0.8 yrs) (median =6.0 years). The protocol was approved by the University at Buffalo Health Science Institutional Review Board and all participants provided written informed consent prior to participation.

Study Protocol

At both the baseline and follow-up examinations all participants underwent a standardized clinical examination that included resting blood pressure, measures of height, weight, and waist girth according to standardized protocols (24,25). Body mass index was calculated as weight in kilograms divided by height in meters squared. Sagittal girth (the distance between the subject's back and the front of the subject's abdomen) was measured with the subject in a supine position using a Holtain-Khan Abdominal Caliper. Three measurements were taken and recorded to the nearest 0.1 cm and the average of the last two used: for accuracy it was confirmed that all three measurements were within 0.5 cm of each other. Hypertension was defined as a resting systolic pressure ≥ 140 mmHg or diastolic pressure ≥ 90 mmHg (both were measured three times and the average of the last two used) and/or taking antihypertensive medications. At both exams study participants were asked to provide a fasting (at least 10 hrs overnight) blood sample and refrain from smoking and vigorous physical activity for 24 hours prior to their appointment and their adherence was validated at each exam prior to their blood draw. Several standardized questionnaires were administered including physical activity (Stanford 7-Day Recall)(26), general health and well-being, personal and family health history, medication use, and socioeconomic status. Current alcohol consumption was defined as reported use of any type of alcoholic beverage in the 30 days preceding the interview. A family history of Type 2 diabetes was defined as a positive report in a first degree relative. Participants were instructed to bring all medications to the clinic visits permitting identification of oral medications as well as insulin use.

Baseline smoking status was ascertained by asking participants if they smoked more than 100 cigarettes in their lifetime. Participants who answered "no" were considered "never smokers" and people who smoked >100 cigarettes but did not currently smoke were categorized as "former smokers." Persons who had not quit were defined as "current smokers." Lifetime total pack-years was assessed by asking participants about the number of packs of cigarettes smoked per day in each decade of life up to their current age. Total lifetime pack-years equals the number of packs smoked per day multiplied by the number of years smoked in each decade of life summed across all decades. Lifetime total pack-years is a measure of smoking intensity, combining duration and frequency. Lifetime pack-years was examined separately among current and former smokers: each smoking category was dichotomized based upon the median number of pack-years smoked (23 and 12 pack-years, respectively). The primary endpoint of interest was incident IFG defined as a subject with normal fasting plasma glucose (FPG) < 100 mg/dl at the baseline examination and FPG ≥ 100 mg/dl and ≤ 125 mg/dl at the follow-up visit (n=101). Because of the small number subjects who converted from normoglycemia (the at risk population identified) to Type 2 diabetes at follow-up (n=6), incident Type 2 diabetes is not herein reported.

Laboratory Methods

Fasting glucose concentrations were determined by the glucose oxidase method (Beckman instruments, Fullerton, CA). The interassay coefficient of variation (CV) was below 5%.

Statistical Procedures

Outcome measures were compared between subjects who progressed to IFG and those who remained normoglycemic (NGT). Categorical variables were compared with χ^2 tests and continuous variables by t tests or analysis of variance. The cumulative incidence of IFG was calculated as the number of subjects who converted from normoglycemia to IFG over the follow-up period divided by the population at risk over the follow-up period (101/924). Logistic regression was utilized to estimate the Odds Ratio (OR) (95% CI) of smoking status (former or current vs. never) on incident IFG after adjustment for age (continuous) sex (male vs. female), sagittal girth (continuous), and family history of T2DM (no/yes). Fasting glucose (continuous) was also included to account for potential residual confounding (Model 1). In Model 2 hypertension (no/yes) was considered in addition to the covariates included in Model 1. The OR (95% CI) of IFG is shown for each category of smoking status compared to never smokers. Additionally, the OR of incident IFG was estimated according to the median lifetime total pack-years smoked within each smoking category. The p-value for trend was calculated using categories of pack-years as a score variable. Likelihood ratio tests were conducted to test for statistical interactions. No significant effect modification was noted. The population attributable risk percent of IFG due to cigarette smoking was calculated using Levin's equation: $P_e(RR-1)/P_e(RR-1)+1 \times 100$ where P_e is the prevalence of the exposure (former and current smoking) in the cohort ($a+b/T$) and where RR is $a/a+b$ divided by $c/c+d$. (27,28). All statistical tests were two-sided and a p-value <0.05 was considered statistically significant. Analyses were carried out using the SPSS for Windows version 14.0 (Chicago, IL).

RESULTS

At baseline there were 924 normoglycemic subjects: 101 progressed to IFG over an average follow-up of 5.9 ± 0.8 years (median 6.0 years). The cumulative incidence of IFG was 10.9%. (Table 1) At baseline, compared to participants who remained normoglycemic converters to IFG were older (58.1 vs. 54.8 yrs, $P=0.006$) had a larger mean BMI (28.1 vs. 26.6 kg/m², $P=0.004$), waist circumference (92.0 vs. 86.1 cm) and sagittal girth (21.3 vs. 19.8 cm) ($P<0.001$ for both). Converters to IFG had a higher fasting glucose than those who remained normoglycemic (94.2 mg/dl vs. 90.3 mg/dl, $P<0.001$). Converters to IFG were more likely than non-converters to currently smoke at baseline (16.8% vs. 11.4%) and less likely to have never smoked (36.6% vs. 50.3%) ($P=0.032$). Moreover, converters to IFG smoked longer (25.6 vs. 22.3 years, $P=0.05$) and more pack-years (15.3 vs. 9.2, $P=0.01$) compared to subjects who remained normoglycemic. A family history of T2DM was more prevalent among converters to IFG than subjects who remained normoglycemic (40.9% vs. 30.2%, $P=0.036$) as well as hypertension (36.7% vs. 21.2%, $P=0.001$).

Table 2 presents the mean (sd) or percentage of baseline characteristics by smoking status. Current smokers were younger ($P=0.019$) and had a smaller BMI ($P=0.003$) and waist circumference ($P=0.001$) compared to never and former smokers. Former smokers had the largest mean sagittal girth ($P<0.001$). There was no significant difference in FPG or physical activity. The lifetime total pack-years smoked was 70% greater among current smokers compared to former smokers and the duration of smoking was twice as long among current vs. former smokers ($P<0.001$ for both). Men were more likely to smoke than women, but a greater proportion of current smokers were female ($P=0.039$). Current smokers were less educated, more likely to be a minority, and female. Never smokers were least likely to report current alcohol consumption ($P=0.04$).

Table 3 shows the OR (95% confidence interval) of developing IFG compared to remaining normoglycemic over the follow-up period according to baseline smoking status. In model 1, adjusted for age (continuous), FPG (continuous), sagittal girth (continuous), family history of T2DM (yes vs. no) and sex (male vs. female) compared to never smokers the OR of IFG among

former smokers was 1.54 (95% CI: 0.93, 2.60) and among current smokers it was 2.36 (95% CI 1.20, 2.46, $P_{trend}=0.01$). With the addition of hypertension (Model 2) the OR was slightly heightened among former smokers OR 1.68 (95% CI: 0.99, 2.80), but unchanged for current smokers OR 2.35 (95% CI: 1.17, 4.72, $P_{trend}=0.008$). Inclusion of alcohol consumption in the models had no material effect on the ORs.

We assessed the effects of duration and intensity (total lifetime pack-years) on the development of IFG. Figure 1 shows the OR of IFG among former and current smokers compared to never smokers stratified by their respective median number of pack-years smoked (12 and 23 pack-years, respectively). Compared to never smokers, the OR of IFG among former smokers with < 12 pack-years was 1.21 (95% CI :0.67, 2.19) and 2.03 (95% CI :1.19,3.44) with ≥ 12 . Compared to never smokers, among current smokers with < 23 pack-years the OR of IFG was 1.91 (95% CI: 0.84, 4.33) and ≥ 23 the OR was 2.14 (95% CI :0.97,4.71) ($P_{trend}=0.004$)

DISCUSSION

This community- based prospective study of middle-aged and older men and women from Erie and Niagara Counties in NY is among the first to show that smoking was associated with an increased risk of incident IFG over a 5.9 year follow-up period. The elevated risk extended to both former and current smokers: former smokers carried about a 60% excess risk of developing IFG and current smokers had 2.5 times greater likelihood of incident IFG compared to never smokers. The significant positive linear trend suggests a dose-dependent association between IFG and smoking even after adjustment for several putative risk factors for T2DM including visceral adiposity, family history, age, glucose, sex, and hypertension. Furthermore, in an analysis that combined dosage and duration (lifetime total pack-years) in conjunction with smoking status we noted that the OR of IFG was similar between former smokers whose total lifetime pack-years was > median and current smokers whose lifetime pack-years was < median, suggesting that the deleterious effects of past smoking did not dissipate over the six years of follow-up. We also showed an elevated risk among all smokers but highest among current heavy smokers.

Only two other studies have examined the association between smoking and IFG, both restricted to men. Among 1,266 Japanese male office workers (35–59 years) prospectively followed for five years, current smokers of ≥ 40.1 pack-years had an RR of IFG that was 2.01 (95% confidence interval 1.05,3.83) compared to never smokers(19). Contrastingly, a cross-sectional study of > 3,000 Japanese male self-defense workers (46–59 years, 98% between 50 and 54 years) found no association between cigarette smoking (past or current) and IFG, IGT, or T2DM (20) perhaps due to the study design, the narrow age range, or the select occupational cohort.

A number of mechanisms linking cigarette smoking to glucose metabolism have been proposed. Experimental studies have shown that smoking may impair insulin action mainly due to a lower peripheral glucose uptake leading to an insulin resistant state (29–31). The mechanism(s) whereby smoking decreases insulin sensitivity remains a source of speculation. One explanation is that cigarette smoke may have a direct toxic effect on the endothelial lining of blood vessels which may lead to increased insulin resistance (23). Moreover, it is well known that smoking is associated with chronic inflammation which is shown to be predictive of Type 2 diabetes. (32–39)

Another hypothesis is that smoking may mediate disturbed glucose metabolism by promoting or inducing alteration in fat distribution. In cross-sectional and longitudinal studies smokers have been shown to be thinner than non-smokers (40,41). Shimokata showed that the hip circumference was smaller in smokers than non-smokers, but the waist-to-hip ratio was greater

in the smokers and increased progressively with the number of cigarettes smoked daily, suggesting that weight is differentially distributed in non-smokers and smokers and more centrally deposited in the smoking group (42). Evidence supporting this was demonstrated in our prospective data: there was a positive linear trend in waist circumference sagittal girth and waist-hip ratio by ascending pack-year category, but no difference in BMI (data not shown). The android pattern of fat deposition is a known risk factor for insulin resistance and diabetes (43–46).

Fifty-one percent (473/924) of subjects in the Western New York Health study smoked (former and current). Compared to non-smokers the crude RR (64/473 divided by 37/451) of IFG among former and current smokers combined was 1.65 (95% confidence interval: 1.29, 2.11). If the relationship between smoking and IFG is causal and if the effect of the exposure were irreversible our results suggest that about 25% (95 confidence interval: 19.2, 30.8) of incident IFG in the total population may be attributed to smoking and would have been preventable if smoking had never been initiated.

The strengths of this study include its population-based, prospective design, and the detailed exposure assessment. Also, we included men and women with a wide age range (35–79 years). One limitation to this study is that the vast majority of participants were White accordingly these results cannot be generalized to minority populations. Further studies in such populations are warranted because minority populations are at high risk for diabetes and some minority groups have a high prevalence of smoking behavior (47). Limitations also include the use of one fasting plasma glucose measure at the baseline and follow-up examinations to identify and categorize normoglycemic and IFG subjects. Reliance on a single measure could have resulted in misclassification: the directionality of the potential bias is unknown. Nevertheless the American Diabetes Association supports the use of one fasting measure (48) in epidemiologic studies partly because it is quicker, easier, and cheaper to obtain than an oral glucose tolerance test (OGTT), and also because it has less intra-individual variation than an OGTT (49–52). Our own data show that the correlation coefficient between baseline and follow-up glucose measures was $r=0.60$.

In summary this prospective, community based study, showed that the risk of incident IFG was associated with smoking status and intensity in a dose-dependent fashion. The mechanism (s) of action whereby cigarette smoking mediates disturbed glucose metabolism is likely multifactorial and requires additional study. Although IFG is not a clinical entity these results support the need for early identification of those at risk to develop diabetes, namely smokers. A recent NHIS report released by the CDC revealed that one-fourth of U.S. adults self-reported that they had pre-diabetes (IFG or IGT); when questioned about risk reduction behaviors i.e. weight loss, physical activity, or reduced fat or calories 42% engaged in one of these behaviors. (53). Notably absent was information on smoking which continues to be a significant public health concern contributing to a large proportion of chronic diseases.

List of Abbreviations and Acronyms

T2DM	Type 2 diabetes mellitus
FPG	Fasting plasma glucose
IFG	Impaired fasting glucose
IGT	

	Impaired glucose tolerance
OGTT	Oral glucose tolerance test
NGT	Normoglycemia
BMI	Body mass index
HTN	Hypertension
RR	Relative risk
OR	Odds Ratio
AR	Attributable risk
CI	Confidence interval
PA	Physical activity

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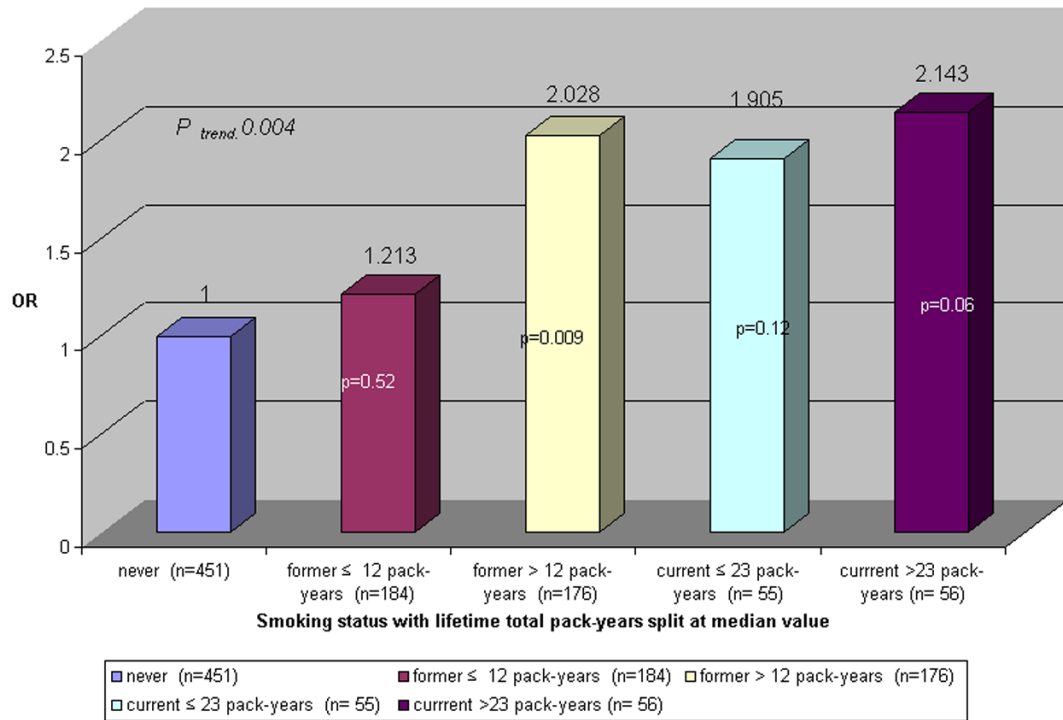


FIGURE 1.
OR of IFG by baseline smoking status with lifetime total pack-years compared to never smokers

Table 1

Mean (standard deviation) or N(%) of Baseline Characteristics According to Conversion Status at Follow-up among Participants in the Western New York Health Study (1996–2004).

	Normoglycemic <i>n</i> =823 <i>Mean(SD)</i>	Impaired Fasting Glucose <i>n</i> =101	P-value
Age (years)	54.8(11.2)	58.1 (11.1)	0.006
BMI (kg/m ²)	26.6(4.8)	28.1(5.1)	0.004
Waist (cm)	86.1(13.1)	92.0 (13.1)	<0.001
Sagittal girth (cm)	19.8(3.3)	21.3 (3.2)	<0.001
Fasting glucose (mg/dl)	90.3 (5.6)	94.2(4.4)	<0.001
⁴ Physical activity	1.4(1.7)	1.4 (2.0)	0.95
Lifetime total pack-years	9.2 (15.3)	15.3 (22.8)	0.01
Duration of smoking (years)	22.3(13.9)	25.6 (15.0)	0.05
	N (%)		
Male	275 (33.4)	45 (44.6)	0.034
White, non-Hispanic	779 (94.7)	96 (96.0)	0.55
Formal education ≥ 12 years	534 (64.9)	61 (60.4)	0.37
Family history of T2DM	239 (30.2)	38 (40.9)	0.036
¹ Hypertension	171 (21.2)	36 (36.7)	0.001
Current drinking	572 (70.2)	63 (62.4)	0.11
Smoking:			0.027
Never	414 (50.3)	37 (36.6)	
Former	315 (38.3)	47 (46.5)	
Current	94 (11.4)	17 (16.8)	

⁴Physical activity in hrs/day ≥ moderate activity.

¹Hypertension defined as SBP≥140 or DBP≥90 and/or taking anti-hypertensive medication

Table 2

Baseline Characteristics by Smoking Status

Baseline characteristic	Never (n=451)	Former (n=362)	Current (n=111)	P-value
	Mean (SD)			
Age (years)	54.5 (11.3)	56.4 (11.0)	53.5 (11.2)	0.019
BMI (kg/m ²)	26.5 (4.6)	27.4 (5.1)	25.9 (4.8)	0.003
Waist (cm)	85.5 (12.8)	88.7 (13.7)	85.1 (13.0)	0.001
Sagittal girth (cm)	19.6 (3.1)	20.6 (3.4)	19.7 (3.3)	<0.001
Fasting glucose (mg/dl)	90.4 (5.72)	91.0 (5.5)	91.0 (5.5)	0.31
Physical Activity (hrs)	1.0 (1.3)	1.0 (1.4)	1.3 (1.8)	0.11
Lifetime total number packs	0.0 (0.0)	6027 (6493)	10216 (6665)	<0.001
Lifetime total pack-years	0.0 (0.0)	16.5 (17.8)	28.0 (18.3)	<0.001
Smoking duration (years)	0.0 (0.0)	18.7 (12.1)	36.0 (11.5)	<0.001
%				
Male	30.6	39.0	36.9	0.039
Whites	95.6	95.9	88.3	0.004
Education >12 years	67.6	58.0	56.0	<0.001
Family history of diabetes	31.5	30.3	34.3	0.74
Hypertension	21.5	24.7	22.2	0.55
Current drinker	65.6	73.9	69.4	0.04

Table includes only those who were normoglycemic at baseline. HTN 140/90 and/or medication Some variables have missing data.

Physical Activity- hours per day in \geq moderate activity

Table 3
Multivariate Adjusted OR (95%CI) of Incident IFG

	Model 1	Model 2
Never	1.0	1.0
Former	1.54 (0.93, 2.60)	1.68 (0.99, 2.80)
Current	2.36 (1.20, 4.60)	2.35 (1.17, 4.72)
<i>P trend</i>	0.01	0.008

Model 1 age (years), family history (yes/no), glucose (mg/dl), sex, sagittal girth (cm)

Model 2, model 1 plus HTN (yes/no)