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ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE AND BIOMARKERS OF CARDIOVASCULAR DISEASE IN NHANES 1999-2006

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M.D., Addis Ababa University Faculty of Medicine, 1987

Thesis Committee Chair: Anne Riederer, Sc.D.

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ABSTRACT

Background: Exposure to environmental tobacco smoke (ETS) is among the leading causes of preventable poor health and premature death in the developed world. Current knowledge pertaining to the association between ETS exposure and early biomarkers of cardiovascular disease is limited.

Objective: This study's purpose was to investigate the association between ETS exposure and the target biomarker concentration.

Methods: Using data from 1996-2006 U.S. National Health and Nutrition Examination Survey (NHANES), adult (≥20 years) non-smokers were selected for analysis (N=4,986). We used weighted multiple linear regression to investigate the association between the target biomarker concentration and ETS exposure, controlling for other predictors of cardiovascular disease risk (diabetes, hypertension, high cholesterol, obesity, and physical activity status). We defined ETS exposure as either self-reported ETS exposure at home or serum cotinine tertile and tested these in separate models.

Results: In the homocysteine models, the regression coefficient of the ETS exposure at home variable was statistically significant and the β coefficient (95% confidence interval) of the ETS term was 0.48 (0.02, 0.95), *p*-value =0.04. In the cotinine model, the β for the cotinine categories were 0.34 (0.06, 0.63), *p* =0.02 for the high category and -0.02 (-0.29, 0.25), *p*-value=0.88 for the moderate category. The ETS variable coefficients were not statistically significant in the c-reactive protein models.

Conclusions: We found significant associations between ETS exposure and serum homocysteine, an early biomarker of cardiovascular risk, in a large, representative sample of U.S. adult non-smokers. These findings build on previous studies reporting significant associations and illustrate the need for continued public health strategies to control ETS exposure.

Key words: homocysteine, c-reactive protein, cotinine, ETS, NHANES

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ABBREVIATIONS

BMI	body mass index
CDC	Centers for Disease Control
CRP	c-reactive protein
CVD	cardiovascular disease
EPA	Environmental Protection Agency
ETS	environmental tobacco smoke (secondhand smoke)
HCY	homocysteine
HDL	high density lipoprotein
NHANES	National Health and Nutrition Examination Survey
OEHHA	Office of Environmental Health Hazard Assessment
SAS	statistical analysis software
SUDAAN	survey data analysis
USDHEW	U.S Department of Health, Education, and Welfare
USDHHS	U.S. Department of Health and Human Services
WHO	World Health Organization

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INTRODUCTION

The tobacco plant is believed to be indigenous to America and has been consumed by Native Americans since time immemorial. Following the exploration of Columbus, colonists adopted its wide use and cultivation throughout the Americas. Explorers introduced it to Europe upon their return by the early part of the 16th century, which resulted in its ubiquitous use throughout the world (U.S Department of Health, Education, and Welfare (USDHEW), 1964).

Doctor Hinds, in his 1882 book, stated, "Tobacco is more universally used among mankind than any other thing except the most ordinary articles of food" (Hinds, 1882). Although, he refrained to put a number tag on the magnitude of tobacco consumption for logistics reason, one can imagine how significantly high it had been then. The trend has continued to increase exponentially to the present day and despite the achievements of the 20th century, it has been reported that an estimated 19.0 % (43.8 million) U.S. adults smoke cigarettes at present (U.S. Centers for Disease Control and Prevention (CDC), 2012).

Following the introduction of tobacco to Europe, its wide spread use was influenced by cultural, medicinal, recreational and religious values. The rapid shift from other forms of tobacco use to cigarette smoking took place by the end of World War I. This was the time when tobacco spitting was blamed for the wide spread of tuberculosis, hence became socially unacceptable and local ordinances were enacted accordingly (USDHEW, 1964). In parallel with the increasing production and use of tobacco, especially with the constantly increasing habit of smoking of cigarettes throughout the world and notably in the Americas, the use of tobacco has become intensively controversial with profound political and economic implications.

By the turn of the 20th century, scientists have become increasingly interested in the effects of tobacco on health and began scientific investigations. In 1964, the U.S. Surgeon

General released its first and exclusive report on smoking and health, specifically on active smoking (USDHEW, 1964). In a sense, the report was a summary of scientific work carried since 1900 based on statistical data. In that report, the Surgeon General presented evidence of a link between smoking and lung cancer and premature death. Accordingly, public health messages called for more investigations and change of life style and habit geared to improving and promoting public health.

Today, a general consensus has been reached on the impact of active smoking on health. Based on a broad experimental and clinical approach, association between smoking and other uses of tobacco and cancer of the lung and of certain other organs, diseases of the heart and blood vessels (cardiovascular diseases in general; coronary artery disease in particular), and the non-cancerous diseases of the lower respiratory tract (especially chronic bronchitis and emphysema), have been demonstrated. The 2004 Surgeon General's report concluded that evidence is sufficient to infer causal relationships on the above associations (U.S. Department of Health and Human Services (USDHHS), 2004). The human and economic losses are vividly outlined in the report, which mentioned that there were 12,000 smoking related deaths since 1964 with economic loss of $157.7 billion each year in the U.S. alone. The report stressed the impact of the tobacco control measures and public health messages which drove adult smoking rates to drop nearly by half between 1965 and 2002, from 42.4 to 22.5 %. Additionally, annual *per capita* consumption of tobacco products has fallen more than half, from 4,345 cigarettes in 1963 to 1,979 cigarettes in 2002 (USDHHS, 2004).

Nevertheless, tobacco smoking remains the leading preventable cause of lung cancer and cardiovascular diseases in the United States, claiming the lives of more than 440,000 Americans each year during 1995-1999 (USDHHS, 2004). A World Health Organization (WHO) report

indicated that tobacco is the second major cause of death and the fourth most common risk factor for diseases worldwide, currently responsible for the death of one in ten adults (about 6 million deaths each year). Based on this, if current smoking patterns continue, we might expect 8 million deaths due to smoking related illnesses each year by 2030 and by the end of the 21st Century, this number could reach one billion (WHO, 2011).

Environmental tobacco smoke (ETS) is a mixture of smoke that comes from the burning end of a cigarette, pipe, or cigar, and smoke exhaled by the smoker (Environmental Protection Agency (EPA), 2013c). Panagitakos *et al*. (2004) reported that ETS is the third leading cause of preventable poor health and premature death in the developed world, next to active smoking and alcohol abuse. The Surgeon General's 2004 report estimated that out of the 440,000 annual deaths attributable to tobacco smoke, around 38,000 are due to ETS causing cancer or cardiovascular disease (CVD) (USDHHS, 2004). ETS causes approximately 3,000 lung cancer deaths per year in the United States (EPA, 2013). Non-smokers, who are exposed to secondhand smoke at home or at work, increase their risks of developing CVD by 25-30% (USDHHS, 2006). In their review of 10 epidemiologic studies, Kritz *et al*. (1995) found a consistent dose-response relationship between ETS exposure and CVD and they estimated that 3,700 cases of CVD per year in the United States are attributable to ETS exposure, accounting for 70% of all deaths caused by ETS exposure. Epidemiological studies have also shown that the risk of ischemic heart disease is about 30% greater in non-smokers who live with smokers than in those who do not (Law *et al*., 1997).

ETS mainly affects indoor settings, because of the tendency of the people of this modern era to spend more time indoors than outdoors. According to EPA, people living in the industrialized nations spend more than 90% of their time in indoors (EPA, 2009a). Infants, the

elderly, those with chronic diseases, and most urban residents of any age may spend even more time indoors. The locations of highest concern are those with prolonged, continuous exposure: homes, schools, and workplaces (EPA, 1995a; Wilson *et al*., 2005).

Pirkle *et al*. (1996) reported that among U.S. children aged 2-11 years, 4% lived in a home with at least 1 smoker, and 37% of adult non-tobacco users lived in a home with at least 1 smoker or reported ETS exposure at work. Ten years later, the Surgeon General reported that almost 60% of U.S. children aged 3-11 years—or almost 22 million children—were exposed to secondhand smoke (USDHHS, 2006). The Surgeon General's report indicated that the geometric mean level of serum cotinine, a biomarker of ETS exposure, fell by 77.1% from 0.293 ng/ml in1988-91 to 0.067ng/ml in 2001-02, with 43% of U.S. non-smokers having detectable serum cotinine in 2001-02 (USDHHS, 2006).

Although the prevalence of ETS exposure and its association with CVD has been well studied, knowledge about the association between ETS and early biomarkers of CVD is limited (Bazzano, 2003; Enstrom, 2006; Iso, 1996; Panagiotakos, 2004). CVD biomarkers include serum levels of the inflammatory mediators, c-reactive protein (CRP) and homocysteine (HCY).

CRP is a hepatically-derived biomarker of atherothrombotic disease and plays a key role in the immune response (Ridker, 2001). In their review, Ridker *et al*. (2003) noted that the relationship between a patient's baseline level of CRP and future vascular risk has been consistent in studies from the United States and Europe, independent of age, smoking, cholesterol levels, blood pressure and diabetes. Magliano *et al*. (2003) and Ridker *et al*. (2003) in their independent reviews of potential biomarkers of CVD, indicated that CRP stands out as the most promising of risk markers of CVD with consistent and reliable results. Its most appealing feature is that it is stable over long period of time, not affected by meals, and

demonstrates no diurnal variation (Ridker *et al*., 2003). However, the major limitation of CRP's use as a biomarker is that it has a tendency to increase up to 100-fold above normal levels in major infections, trauma, or acute hospitalization (Melander *et al*., 2009). In their review of 52 cohort studies, Kaptoge *et al*. (2012) emphasized that assessment of CRP could help prevent one additional vascular event over a period of 10 years for every 400 to 500 people screened.

HCY is an amino acid and intermediate product of the metabolism of methionine and cysteine. The exact mechanism of action with respect to CVD remains unknown, but direct stimulation of the endothelium and lowering high density lipoprotein (HDL) level have been suggested (Magliano *et al*., 2003; Xaio *et al*., 2011). Magliano *et al*. (2003), in their review of previous studies found out a positive association between elevated HCY levels and CVD.

We investigated associations between ETS exposure and serum CRP and HCY using data from the 1999-2006 U.S. National Health and Nutrition Examination Survey (NHANES), designed to assess the health and nutritional status of adults and children in the United States (CDC, 2013a). In addition to serum CRP and HCY, NHANES measures serum levels of cotinine, as an objective measure of ETS exposure. Cotinine, a major metabolite of nicotine, is preferred because of its longer half-life which is estimated to be about 15–20 hours; by contrast, the half-life of nicotine is only 0.5–3 hours (CDC, 2013a). Our overall objective was to determine whether significant associations exist, controlling for other risk factors of cardiovascular disease.

METHODS

Study Design and Data Collection

The data for this study came from the continuous, public release 1999-2006 NHANES. NHANES combines interviews and physical examinations. The interview involves demographic, socioeconomic, dietary, and health-related questionnaires; while the examination component consists of medical, physiological measurements and laboratory tests. For this study, the sample population was restricted to adult (age ≥20), self-reported non-smoking participants who completed the NHANES medical examination.

Statistical Analysis

Data were analyzed using SAS 9.3 (SAS Institute, Cary, North Carolina) and SUDAAN 11.0 (Research Triangle Institute, Research Triangle Park, North Carolina). Demographic, questionnaire and laboratory files with selected variables (age, sex, race / ethnicity, country of birth, education level, marital status, c-reactive protein, homocysteine, total cholesterol, cotinine, BMI, hypertension, diabetes, physical activity, ETS exposure in home / work place) were downloaded and merged to create a master file for the analysis. Sample weights for the eight-year (1999-2006) survey were calculated following CDC (2013b). As a general rule, if 10% or less of the data for a variable is missing, it is acceptable to continue analysis without adjustment (CDC, 2013a). The lab values of HCY, CRP, cotinine and total cholesterol were checked for normality. Serum cotinine was classified into low, intermediate and high based on values below the first tertile, in between the first and third tertiles and above the third tertile respectively. Participants, who reported that they were non-smokers but had serum cotinine measurements ≥15 ng/ml, were excluded as this level is consistent with active smoking status (Venn, 2007). A total of 438 observations were excluded following this criterion. Weighted frequency

distributions and descriptive statistics were calculated using the SUDAAN CROSSTAB and DESCRIPT procedures for the categorical and continuous variables, respectively. The Wald Chi-square Test was used to compare groups.

Univariate and multiple linear regression analyses were conducted using CRP and HCY as separate response variables, with ETS exposure status at home and cotinine as predictors, adjusted for demographic, socioeconomic and co-morbidity variables. ETS exposure and cotinine were used in separate models, to avoid collinearity as concurrent use of these variables might exaggerate the variance of regression parameters and hence potentially lead to the wrong identification of predictors (Dorman *et al.,* 2012). Regression models were fit using the REGRESS procedure in SUDAAN to account for the NHANES sample design. Regression coefficients were calculated for the Other Hispanic and Other race/ethnicity categories; however, since NHANES is not designed to be statistically representative of these categories, these results are not reported (CDC, 2013a). In separate sub-analyses, a variable representing ETS exposure both at work and home was evaluated, but could not be used on the full sub-sample because of the large proportion of missing observations, since many participants reported not working outside the home. Model assumptions (of linearity and normally-distributed, independent error terms) were checked by examining histograms of the residuals and scatter plots of predicted *versus* observed values. A p-value ≤ 0.05 was considered statistically significant for hypothesis tests.

RESULTS

There were a total 41,474 participants in NHANES 1999-2006, of which 4,986 met our selection criteria. Table 1 shows frequencies of missing and non-missing observations for the variables of interest. Missing observations generally did not exceed 10% except for ETS exposure at work, with 41.03% of observations missing due to the skip pattern of the questionnaire and its application only to those who currently had a job. Table 2 shows descriptive statistics of the restricted sample: 55.67% were male, 80.1% were white, 43.88% had high school or less education, 94.08% had a family income above the poverty threshold, 72.43% lived with either a spouse or a partner, 9.63% were diabetics, 72.53% were either overweight or obese, 53.49% reported engaging in moderate physical activity in the past month, 36.10% had a diagnosis of hypertension and 8.47% reported being exposed to ETS at home.

The mean age of the selected participants was 53.6±28.4 years (Table 3.). The geometric mean concentrations of the biomarkers of interest are also shown in Table 3. Sex, BMI status, physical activity status, educational level and economic status were statistically significantly different between those reporting ETS exposure at home *versus* those who reported no ETS exposure at home (Table 4). Participants who reported ETS exposure at home had statistically significantly higher geometric mean levels of HCY (8.94±0.03 umol/L). Geometric means of CRP and total cholesterol were 0.26±0.08 mg/dL and 204.38±0.02 mg/dL, respectively, with no statistically significant difference between those reporting ETS exposure at home *versus* those who did not (Table 5). Figures 1 and 2 are scatter plots of log HCY *versus* log cotinine and log CRP *versus* log cotinine, respectively, showing no strong pattern of association between cotinine and either CVD biomarker.

Tables 6-11 present the results of the regression analyses. In the HCY analyses, the adjusted R^2 values were 0.28, 0.20 and 0.28 for the ETS exposure at home, ETS exposure at both home and workplace and serum cotinine models, respectively. For CRP, the adjusted R^2 values were 0.10, 0.13 and 0.10 for the ETS exposure at home, ETS exposure at both home and workplace and cotinine models, respectively. All the HCY models had adjusted R^2 values ≥ 0.2, indicating reasonable fit to the data. On the other hand, all the CRP models showed poor fit to the data (adjusted $R^2 \leq 0.2$). Scatter plots of the residuals and plots of predicted *versus* observed values (Figures 1-14) indicate that model assumptions of normality and homoscedasticity were not violated.

The three HCY regressions showed statistically significant associations between the ETS exposure variable(s) and HCY, adjusting for age, sex, race, education level, marital status, country of birth, family income, BMI, blood pressure status, diabetes status, moderate physical activity status and total cholesterol level. In the ETS exposure at home (yes/no) model, the regression coefficient (β) (95% confidence interval) of the ETS term was 0.48 (0.02,0.95), *p*-value =0.04 (Table 6). In the cotinine model, the βs for the cotinine categories were 0.34 (0.06, 0.63), *p* =0.02 for the high category and -0.02 (-0.29, 0.25), *p*-value=0.88 for the moderate category (Table 7). In the combined ETS exposure at home and workplace model, the β of the ETS term was -0.45 (-1.2, 0.29), *p*-value=0.23 (Table 8). Among the covariates, total cholesterol, race, family income, and education level were not significantly associated with serum HCY, while sex and hypertension were significantly associated with serum HCY.

None of the three CRP models showed statistically significant associations between CRP and the ETS exposure terms. Sex and hypertension were significantly associated with CRP, as they were in the HCY models. In the ETS exposure at home (yes/no) model, the β of the ETS

term was 0.03 (0.05, 0.12), *p*-value =0.43 (Table 9). In the combined ETS exposure at home and workplace model, the β of the ETS term was 0.32 (0.04, 0.60), *p*-value=0.03 (Table 10). In the cotinine model, the βs of the cotinine categories were 0.03 (-0.02, 0.09), *p*-value =0.19 for the moderate category and 0.06 (-0.02, 0.13), *p*-value =0.13 for high category (Table 11).

DISCUSSION

In this cross sectional study, associations between ETS and two biomarkers of CVD, serum HCY and CRP, were examined in adult non-smokers using NHANES 1999-2006 data. We tested two different measures of ETS exposure—ETS exposure at home (yes/no) and serum cotinine tertile—in separate regression analyses. In these models, we controlled for important CVD risk factors, including age, sex, race / ethnicity, country of birth, education level, marital status, total cholesterol, BMI, hypertension, diabetes and physical activity. We also conducted a sub-analysis including a variable representing ETS exposure both at home and at work using the more limited number of participants who reported working outside the home. We found statistically significant, positive associations between ETS exposure and serum HCY in both the ETS exposure at home and serum cotinine models, but not the ETS exposure at home and work model. In the CRP models, we found a statistically significant, positive association between ETS exposure at home and work and serum CRP, but the associations in the ETS exposure at home and serum cotinine models were not statistically significant.

Our findings are consistent with those of other researchers who found associations between ETS exposure or active smoking and CVD biomarkers. Venn *et al.* (2004), based on NHAHES III data, investigated the association between ETS exposure (measured by cotinine), and CRP, HCY, fibrinogen, and white blood cell count. Compared with participants with no

detectable cotinine, those with detectable but low-level cotinine (range, 0.05 to 0.215 ng/mL) had significantly higher levels of both fibrinogen (adjusted mean difference, 8.9 mg/dL; 95% CI, 0.9 to 17.0; p=0.03) and HCY (0.8 umol/L; 95% CI, 0.4 to 1.1; p<0.01) but not CRP or white blood cell count. Our findings were consistent with their report on CRP and HCY, but comparison cannot be made with their findings of fibrinogen and white cell counts as our study did not include these biomarkers. Bazzano *et al.* (2003) also used the NHANES III data to study the relationship between active smoking and biomarkers of CVD and reported that smokers had higher levels of CRP, fibrinogen, and HCY compared with non-smokers. Panagiotakos *et al.* (2004), in their case-control study, reported significantly higher odds of developing acute coronary syndrome in participants who were exposed to ETS *versus* those who were not. In their Oslo II study, Madesen *et al.* (2007) found a positive dose-response relationship between the amount of current cigarette smoking and elevated CRP levels, compared to occasional or non-smokers.

In our models, HCY levels were significantly lower in females than in males, likely due to the influence of estrogen (Christodoulakos *et al.*, 2006). On the other hand, CRP levels were higher in females than males, due to adiposity as a contributor of subclinical inflammation (Khera *et al.*, 2009). Diabetic patients tend to have lower HCY (Matetzky *et al.* 2003), but we found higher levels in diabetic non-smokers than in non-diabetic non-smokers.

Limitations. NHANES data are cross-sectional; hence do not reveal causal associations between ETS exposure and CVD risk. Our study only examined two early biomarkers of CVD. The other potential biomarker with promising role in predicting CVD events is fibrinogen (Bazzano *et al.*, 2003). Fibrinogen data were complete only for those over age 40 and only for NHANES 1999-

2001 survey, thus we could not include it in this study. Another limitation is that our models only explained 20-28% and 10-13-% of the variance in the HCY and CRP data, respectively.

CONCLUSIONS

Despite our study limitations, we found significant associations between ETS exposure and serum HCY, an early biomarker of CVD risk, in a large, representative sample of U.S. adult non-smokers. These findings build on previous studies reporting significant associations. Although local ordinances restricting smoking in public places have helped reduce ETS exposure throughout the United States (OEHHA, 2005), ETS exposure may still increase CVD risk. Education and outreach activities aimed at reducing smoking in the home and elsewhere are important public health tools for helping lower this risk.

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TABLES

Table 1. Unweighted frequencies (weighted %) of missing and non-missing observations, adult (age≥20) non-smokers, NHANES 1999-2006 (N=4,986)

Variable	n (%) missing	n (%) non-missing
Blood pressure status	20 (0.35)	4,966 (99.65)
BMI	159 (2.55)	4,827 (97.45)
Cholesterol	285 (4.98)	4,701 (95.02)
Country of birth	2 (0.04)	4,986 (99.96)
Cotinine	317 (5.58)	4,669 (94.42)
CRP	266 (4.69)	4,720 (95.31)
Diabetes status	106 (1.61)	4,880 (98.39)
Education level	9 (0.12)	4,977 (99.88)
ETS exposure at home	42 (0.71)	4,944 (99.29)
ETS exposure at work	2,645 (41.03)	2,341 (58.97)
Family PIR	394 (6.75)	4,592 (93.25)
Homocysteine	244 (4.34)	4,742 (95.66)
Marital status	124 (2.96)	4,862 (97.04)
Physical activity status	2 (0.05)	4,984 (99.95)
Race, age and sex	0 (0.00)	4,986 (100.00)

BMI= body mass index. CRP = C-reactive protein. ETS = environmental tobacco smoke. PIR = family poverty income ratio.

Table 2. Weighted response frequencies of selected categorical variables, adult (age≥20) non-smokers, NHANES 1999-2006 (N=4,986)

Variable	Frequency	Weighted frequency	SD of weighted frequency	Percent	SE of percent	95% CL for percent	
Sex							
Male	2,927	28,343,457	1,121,838	55.67	0.87	53.94	57.41
Female	2,059	22,567,556	1,051,484	44.33	0.80	42.60	46.06
Race/ethnicity[a]							
Mexican American	981	2,960,320	290,350	5.81	0.65	4.51	7.12
White	2,984	40,780,116	2,069,770	80.10	1.35	77.40	82.80
Black	728	3,476,736	273,927	6.83	0.67	5.51	8.15
Country of birth							
USA	4,094	44,807,395	1,966,413	88.04	0.91	86.23	89.86
Mexico	512	1,696,779	148,493	3.33	0.34	2.65	4.02
Elsewhere	378	4,387,033	409,261	8.62	0.79	7.03	10.21
Education level							
HS or less	2,711	22,338,754	1,009,867	43.88	1.18	41.51	46.28
Some college	1,316	15,698,818	1,727,614	30.84	0.78	29.27	32.40
College graduate	950	12,810,217	790,679	25.16	1.09	22.97	27.35
Family PIR[b]							
< 1	627	4,236,157	286,059	8.92	0.53	7.87	9.98
≥1	3,965	43,239,400	1,818,138	91.08	0.53	90.02	92.13

SD=standard deviation. SE= standard error. CL=confidence limit. HS=high school. PIR= poverty income ratio.

[a]Other Hispanic and Other race/ethnicity categories not shown. [b]based on poverty threshold.

Table 2 (continued). Weighted frequencies of selected categorical variables, adult (age≥20) non-smokers, NHANES 1999-2006 (N=4,986)

Variable	Frequency	Weighted frequency	SD of weighted frequency	Percent	SE of percent	95% CL for percent	
Marital status							
Married[a]	3,342	35,800,541	1,644,469	72.47	0.88	70.71	74.23
Single	1,520	13,601,239	663,479	27.53	0.88	25.77	29.29
BP status							
High	2,013	18,313,733	799,959	36.10	0.95	34.20	37.99
Normal	2,953	32,421,626	1,422,458	63.90	0.95	62.01	65.80
Diabetes							
Yes	661	4,821,356	316,409	9.63	0.49	8.65	10.60
No	4,219	45,269,422	1,797,277	90.37	0.49	89.40	91.34
BMI[b]							
<25	1,251	13,626,805	658,753	27.47	0.73	26.01	28.92
≥25	3,576	35,984,504	1,410,290	72.53	0.73	71.08	73.99
Moderate activity							
Yes	2,342	27,217,303	1,286,628	53.49	1.02	51.45	55.53
No	2,642	23,667,496	949,923	46.51	1.02	44.47	48.55
Does anyone smoke in the home							
Yes	429	4,282,332	304,033	8.47	0.57	7.32	9.62
No	4,515	46,266,731	1,898,636	91.53	0.57	90.38	92.68

BMI= body mass index. CL=confidence limit. BP= blood pressure.
[a]Includes those living with partner [b]BMI <25 normal; ≥25 overweight /obese.

Table 3. Weighted descriptive statistics of selected continuous variables, adult (age≥20) non-smokers, NHANES 1999-2006 (N=4,986)

Variable	N	Geometric mean	Geometric SD	95% CL for the geometric mean	
Cotinine[a]					
Low (≤0.023 ng/mL)	1,191(24.3%)				
Moderate (0.023< .0.255 ng/mL)	2,311(49.3%)				
High (>0.255 ng/mL)	1,167(26.4%)				
Homocysteine (umol/L)	4,742	8.49	0.01	8.33	8.66
C-reactive protein (mg/dL)	4,720	0.20	0.03	0.19	0.21
Total cholesterol (mg/dL)	4,701	200.76	0.00	198.90	202.64
Age	4,986	53.60[b]	28.40[b]		

SD= standard deviation. CL=confidence limit.
[a]Frequency (%) . [b]Arithimetic mean and standard deviation.

Table 4. Characteristics of adult (age≥20) non-smokers (weighted % unless noted) by home ETS exposure status, NHANES 1999-2006 (N=4,986)

Characteristic	Does anyone smoke in the home?		*p*-value[a]
	YES	NO	
Age (years)[b]	53.43 ±1.07	54.23 ± 0.45	0.45
Sex			
Male	60.96	52.39	0.04
Female	39.04	47.61	
Educational level			
HS or less	56.13	41.31	<0.01
Some college	30.10	31.34	
College+	13.77	27.35	
Race / ethnicity			
Mexican American	5.15	6.27	0.13
African American	9.44	5.86	
Non-Hispanic White	78.78	80.89	
Marital status			
Live with spouse or partner	74.60	72.89	0.62
Live alone	25.40	27.11	
Place of birth			
Born in US	89.96	87.75	0.26
Born in Mexico	2.24	3.58	
Born elsewhere	7.79	8.67	
Economic status			
Family PIR ≤ 1	12.00	7.73	0.06
Family PIR > 1	88.00	92.27	
Overweight/obesity			
BMI < 25	80.36	72.60	0.01
BMI > 25	19.64	27.40	
Not having moderate physical activity=Yes	52.56	44.82	0.03
ETS exposure at work			
Smell tobacco at work	19.89	16.74	0.45
Co-morbidities			
Ever told you had high pressure=Yes	39.15	36.79	0.51
Doctor told you have diabetes=Yes	12.51	9.70	0.28

HS=high school. PIR=poverty income ratio. BMI= body mass index. ETS=environmental tobacco smoke.

[a]Wald Chi-square Test by ETS exposure at home status. [b]Arithmetic mean and standard deviation.

Table 5. Weighted frequencies (%) by cotinine tertile and weighted geometric mean (geometric standard deviation) concentrations of serum cotinine, homocysteine, c-reactive protein, and total cholesterol among adult (≥20) non-smokers, by ETS exposure status at home, NHANES 1999-2006

Biomarker	Does anyone smoke in the home?		*p*-value
	YES	NO	
Cotinine (ng/mL)			<0.01[a]
Low (≤0.023 ng/mL)	1,184 (99.75%)	3 (0.25%)	
Moderate (0.023< ≤0.255 ng/mL)	2,225 (97.03%)	68 (2.97%)	
High (>0.255 ng/mL)	492 (67.86%)	233 (32.14%)	
Homocysteine (umol/L)	8.94±0.03 (8.42, 9.48)	8.41±0.01 (8.25, 8.58)	0.03[b]
C-reactive protein (mg/dL)	0.26 ±0.08 (0.22, 0.30)	0.20±0.03 (0.19, 0.22)	0.34[b]
Total cholesterol (mg/dL)	204.38 ±0.02 (196.50, 212.60)	200.34±0.00 (200.30, 200.40)	0.34[b]

[a]Student t-test. [b]Chi-square Test.

Table 6. Results of multivariable linear regression of serum homocysteine and ETS exposure at home, adult (≥20) non-smokers, NHANES 1999-2006 (Adjusted R^2= 0.28)

Predictors	Regression coefficient (β)	95% CI	*p*-value
Intercept	5.84	(5.12,1.6.57)	<0.01
Does anyone smoke in the home			
Yes	0.48	(0.02, 0.95)	0.04
No[a]			
Age	0.07	(0.06, 0.08)	0.00
Sex			
Female	-1.16	(-1.86, -1.36)	0.00
Male[a]			
Race/ethnicity			
Mexican American	-0.27	(-0.64, 0.11)	0.16
African American	0.14	(-1.26, 0.54)	0.50
White[a]			
Educational level			
HS or less	0.26	(-0.05, 0.58)	0.10
Some college	0.00	(-0.28, 0.29)	0.97
College graduate[a]			
Marital status			
No (Live alone)	0.36	(0.12, 0.59)	0.00
Yes (Live with spouse/partner[a]			
Country of birth			
Born in Mexico	-0.70	(-1.11, -0.29)	0.00
Born elsewhere	-0.20	(-0.64, 0.25)	0.38
Born in US[a]			
Family PIR			
Yes (≤1)	0.22	(-0.18, 0.61)	0.27
No (>1)[a]			
Overweight/obesity			
Yes (BMI> 25)	-0.09	(-0.33, 0.15)	0.44
No (BMI <25)[a]			
Ever told you had high blood pressure			
Yes	0.67	(0.46, 0.89)	0.00
No[a]			
Doctor told you have diabetes			
Yes	0.80	(0.23, 1.36)	0.01
No[a]			
Not having moderate physical activity			
Yes	0.41	(0.19, 0.63)	0.00
No[a]			
Total cholesterol	-0.00	(-0.00, 0.00)	0.69

CI= Confidence interval. PIR= poverty income ratio. BMI=Body mass index. [a]Referent category.

Table 7. Multivariable linear regression analysis of serum homocysteine by serum cotinine level, among adult (≥20) non-smokers, NHANES 1999-2006 (Adjusted R^2= 0.28)

Predictors	Beta Coefficient	95% CI	p-value
Intercept	5.73	(4.94,6.51)	<0.01
Serum cotinine			
Low: <= 0.023 ng/mL [a]			
Moderate: > 0.023 <= 0.255 ng/mL	-0.02	(-0.29,0.25)	0.88
High: > 0.255 ng/mL	0.34	(0.06,0.63)	0.02
Sex			
Male[a]			
Female	-1.59	(-1.85,-1.32)	< 0.01
Race/Ethnicity			
Mexican American	-0.28	(-0.64,0.09)	0.14
White[a]			
African American	0.12	(-0.29,0.52)	0.56
Education level			
HS or Less	0.26	(-0.04,0.56)	0.09
Some College	0.00	(-0.28,0.29)	0.98
College graduate[a]			
Marital Status			
Yes[a]			
No	0.34	(0.10,0.57)	0.01
Country of Birth			
Born in US[a]			
Born in Mexico	-0.70	(-1.10,-0.30)	0.00
Born elsewhere	-0.20	(-0.66,0.25)	0.37
Family PIR			
Yes	0.21	(-0.19,0.60)	0.31
No[a]			
Overweight or obese			
Yes	-0.09	(-0.33, 0.15)	0.45
No[a]			
Ever told you had high BP			
Yes	0.66	(0.44, 0.88)	0.00
No[a]			
Doctor told you have diabetes			
Yes	0.80	(0.23,1.38)	0.01
No[a]			
Not having moderate physical activity			
Yes	0.42	(0.20,0.64)	0.00
No[a]			
Total cholesterol (mg/dL)	-0.00	(-0.00,0.00)	0.78

CI=confidence interval. HS= high school. BP= blood pressure. PIR= poverty income ratio.
[a]Referent

Table 8. Multivariable linear regression analysis of serum homocysteine by ETS exposure status at home and workplace, among adult (≥20) non-smokers, NHANES 1999-2006 (Adjusted R^2=0.20)

Predictors	Beta Coefficient	95 % Confidence interval	p-value
Intercept	5.81	(4.93, 6.69)	<0.01
ETS exposure at home and/or work			
Exposure at both places	-0.45	(-1.20,0.29)	0.23
Exposure at least at one place	0.14	(-0.23, 0.51)	0.45
No exposure[a]			
Gender			
Male[a]			
Female	-1.51	(-1.87,-1.16)	<0.01
Race/Ethnicity			
Mexican American	-0.12	(-0.50,0.26)	0.54
African American	0.10	(-0.35,0.55)	0.66
White[a]			
Education level			
HS or Less	0.35	(-0.11,0.81)	0.13
Some College	-0.08	(-0.41,0.25)	0.63
College graduate[a]			
Marital Status			
Yes[a]			
No	0.08	(-0.22,0.38)	0.60
Country of Birth			
Born in US[a]			
Born in Mexico	-0.80	(-1.24,-0.36)	<0.01
Born elsewhere	-0.12	(-0.70, 0.45)	0.67
Family PIR			
Yes	-0.04	(-0.55,0.48)	0.89
No[a]			
Overweight or obese			
Yes	-0.01	(-0.29, 0.28)	0.96
No[a]			
Ever told you had BP			
Yes	0.57	(0.28,0.87)	<0.01
No[a]			
Doctor told you have			
Diabetes			
Yes	0.27	(-0.22,0.77)	0.28
No[a]			
Not having moderate PA			
Yes	0.03	(-0.26,0.31)	0.85
No[a]			
Total cholesterol (mg/dl)	0.00	(-0.00,0.00)	0.36
Age	0.06	(0.05,0.07)	0.00

HS = high school. PIR= poverty income ratio. BP= blood pressure. PA=physical activity.
[a]Referent

Table 9. Multivariable analysis of serum c-reactive protein level among nonsmoker adults (≥ 20 years) by ETS exposure at home, NHANES 1999-2006 (Adjusted R^2=0.10)

Predictors	Beta Coefficient	95% Confidence interval	P-value
Intercept	0.10	(-0.02,0.22)	0.11
Does anyone smoke in the home			
Yes	0.03	(0.05,0.12)	0.43
No[a]			.
Gender			
Male[a]			
Female	0.20	(0.14,0.25)	0.00
Race/Ethnicity			
Mexican American	0.07	(0.00,0.15)	0.05
African American	0.05	(-0.02,0.11)	0.14
White[a]			.
Education Level			
HS or Less	0.06	(-0.01,0.12)	0.10
Some College	-0.00	(-0.06,0.06)	0.90
College graduate[a]			.
Marital Status			
Yes	0.00	0.00	.
No	0.04	(-0.01,0.10)	0.12
Country of Birth			
Born in US[a]			
Born in Mexico	-0.18	(-0.26,-0.10)	0.00
Born elsewhere	-0.07	(-0.14,0.00)	0.04
Family PIR			
Yes	0.06	(-0.02,0.14)	0.13
No[a]			.
Ever told you had high BP			
Yes	0.07	(0.02,0.12)	0.01
No			
Doctor told you have DM			
Yes	0.07	(0.02,0.12)	0.01
No[a]			
Not having moderate PA			
Yes	0.07	(0.02,0.12)	0.01
No[a]			.
Total cholesterol (mg/dl)			
	-0.00	-0.00	0.42
Age	0.00	-0.00	0.50

ETS=environmental tobacco smoke. PIR=poverty income ratio. BP=blood pressure. DM=diabetes mellitus. PA=physical activity. [a]Referent.

Table 10. Linear regression analysis of c-reactive protein among adult (≥20) non-smokers by ETS exposure status at home and work, NHANES 1999-2006 (Adjusted R^2=0.13).

Predictors	Beta coefficient	95% confidence interval	p-value
Intercept	0.10	(-0.07,-0.28)	0.38
ETS exposure at home and/or work			
Exposure at both places	0.32	(0.04,0.60)	0.03
Exposure at least at one place	0.03	(-0.04,0.11)	0.39
No exposure[a]			
Sex			
Male[a]			
Female	0.23	(0.15,0.30)	<0.01
Race/Ethnicity			
Mexican American	0.07	(-0.04,0.18)	0.22
African American	0.04	(-0.05, 0.13)	0.39
White[a]			
Education level			
HS or Less	0.04	(-0.04,0.12)	0.32
Some College	-0.00	(-0.08,0.07)	0.92
College graduate[a]			
Marital Status			
Yes[a]			
No	0.03	(-0.04,0.10)	0.43
Country of Birth			
Born in US[a]			
Born in Mexico	-0.17	(-0.27,-0.07)	0.00
Born elsewhere	-0.06	(-0.14,0.02)	0.12
Family PIR			
Yes	-0.02	(-0.08,0.04)	0.58
No[a]			
Overweight or obese			
Yes	0.27	(0.20,0.33)	0.00
No[a]			
Ever told you had high blood pressure			
Yes	0.09	(0.02,0.16)	0.01
No[a]			
Doctor told you have			
Diabetes			
Yes	0.05	(-0.07,0.17)	0.41
No[a]			
Not having moderate PA			
Yes	0.03	(-0.03,0.09)	0.30
No[a]			
Total cholesterol			
(mg/dL)	-0.00	(-0.00,0.00)	0.79
Age	-0.00	(-0.00,0.00)	0.22

ETS=environmental tobacco smoke. HS=high school. PIR=poverty income ratio. PA=physical activity [a]Referent

Table 11. Linear regression analysis of c-reactive protein among adult (≥20) non-smokers by serum cotinine level, NHANES 1999-2006 (Adjusted R^2=0.10).

Predictors Variables and	Beta coefficient	95% confidence interval	p-value
Intercept	0.06	(-0.09,0.21)	0.77
Serum Cotinine level			
Low <= 0.023 ng/mL			
Moderate: > 0.023 <= 0.255 ng/mL	0.03	(-0.02,0.09)	0.19
High: > 0.255 ng/mL	0.06	(-0.02,0.13)	0.13
Sex			
Male			
Female	0.20	(0.15,0.26)	< 0.01
Race/Ethnicity			
Mexican American	0.08	(0.00,0.15)	0.04
African American	0.04	(-0.02,0.11)	0.17
White[a]			
Education			
HS or Less	0.05	(-0.02,0.12)	0.15
Some College	-0.01	(-0.06,0.05)	0.85
College graduate[a]			
Marital Status			
Yes			
No	0.04	(-0.02,0.10)	0.16
Country of Birth			
Born in US[a]			
Born in Mexico	-0.18	(-0.26,-0.10)	0.00
Born elsewhere	-0.07	(-0.14,-0.00)	0.04
Family PIR			
Yes	0.06	(-0.02,.14)	0.15
No[a]			
Overweight or obese			
Yes	0.22	(0.17,0.26)	0.00
No[a]			
Ever told you had high BP			
Yes	0.07	(0.02,0.12)	0.01
No[a]			
Doctor told you have diabetes			
Yes	0.08	(-0.01,0.17)	0.08
No[a]			
Not having moderate PA			
Yes	0.07	(0.02,0.12)	0.01
No[a]			
Total cholesterol (mg/dl)	-0.00	(-0.00,.00)	0.41
Age	0.00	(-0.00,.00)	0.32

HS=high school. PIR=poverty income ratio. BP=blood pressure. PA=physical activity.

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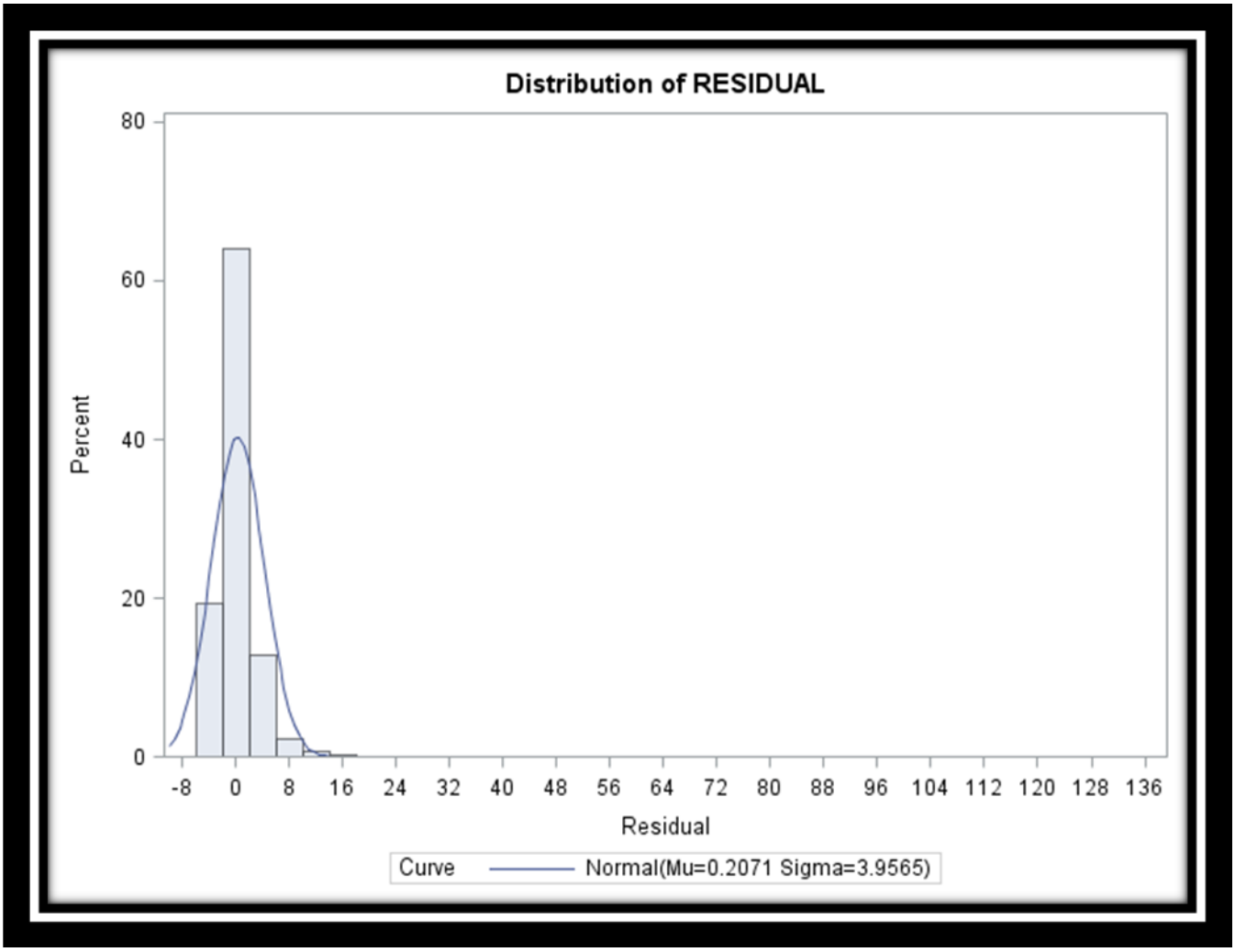

Figure 1. Histogram of residuals from multiple linear regression model of homocysteine and ETS exposure at home

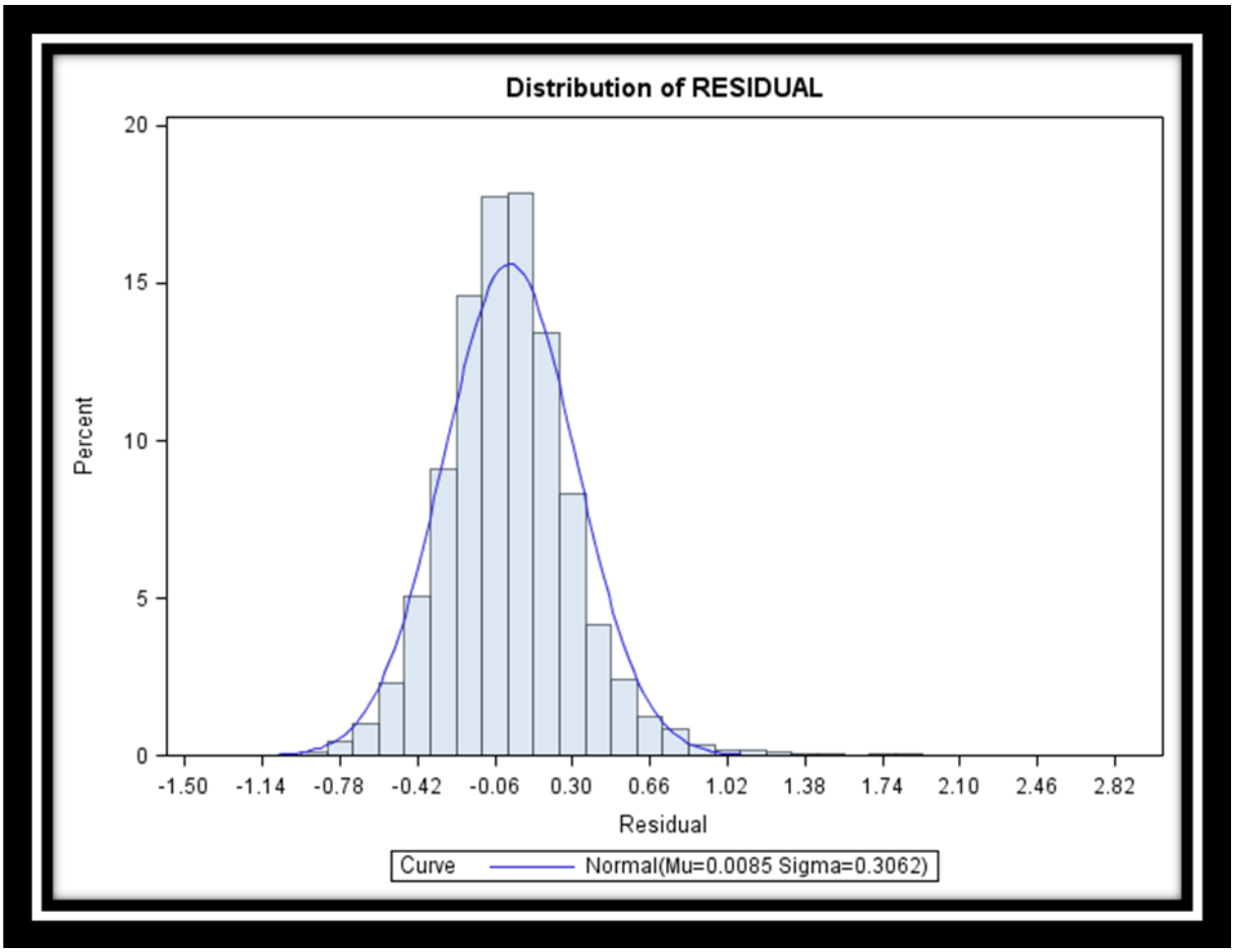

Figure 2. Linear regression model for log Homocysteine, by ETS exposure status at home

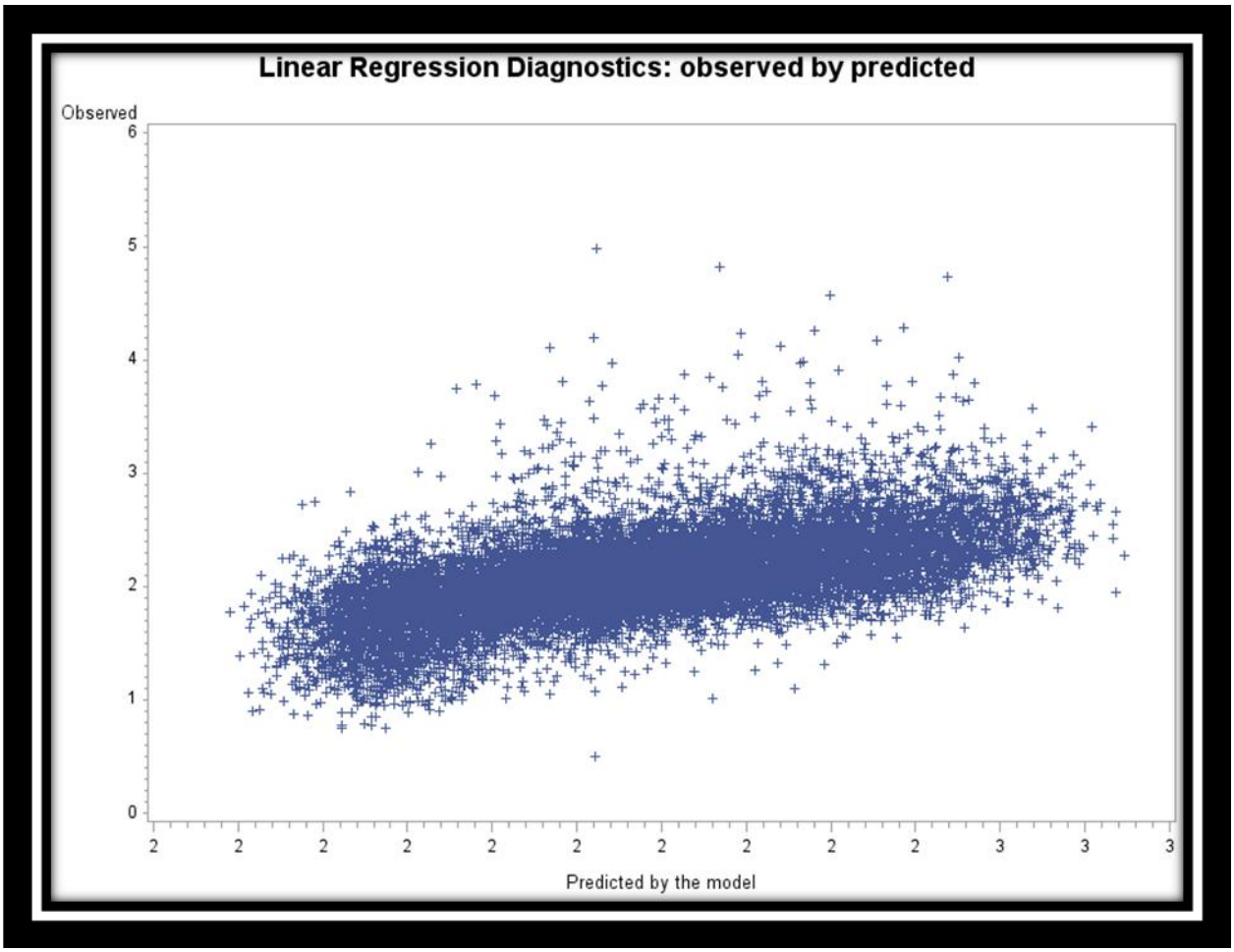

Figure 3. Scatter plot of predicted versus observed values from multiple linear regression of log homocysteine and ETS exposure at home

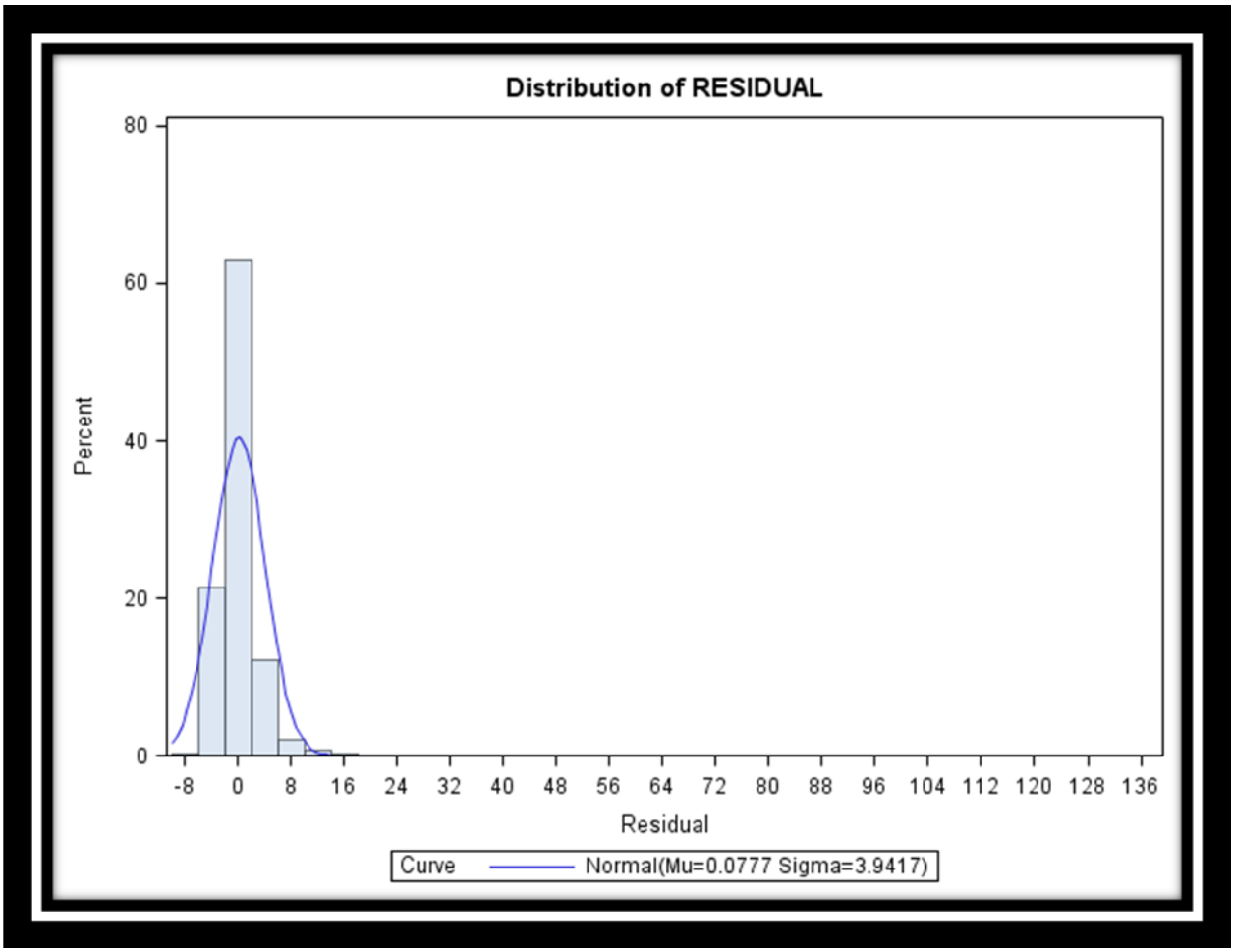

Figure 4. Linear regression model for homocysteine, by serum cotinine category

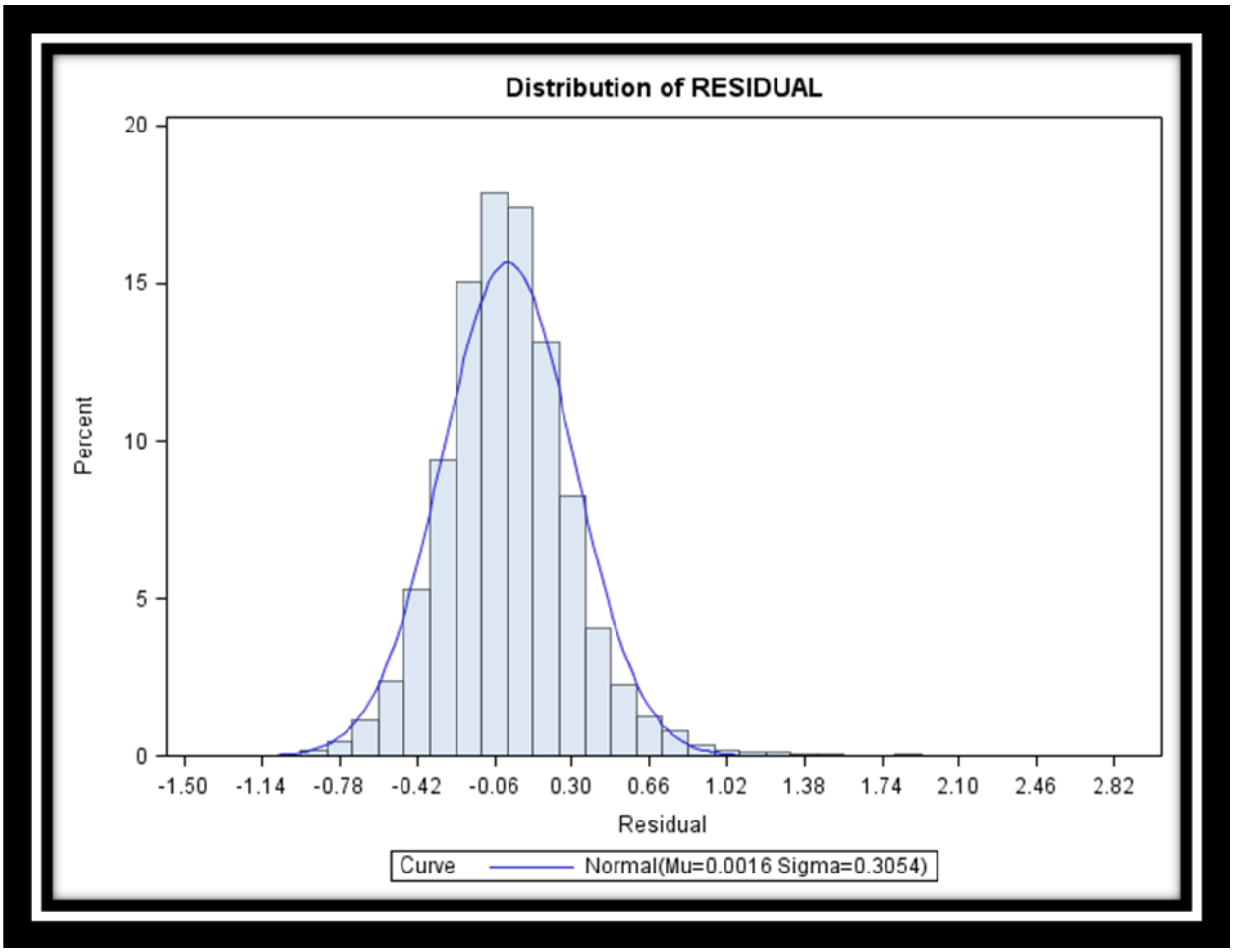

Figure 5. Linear regression model for log homocysteine, by serum cotinine category

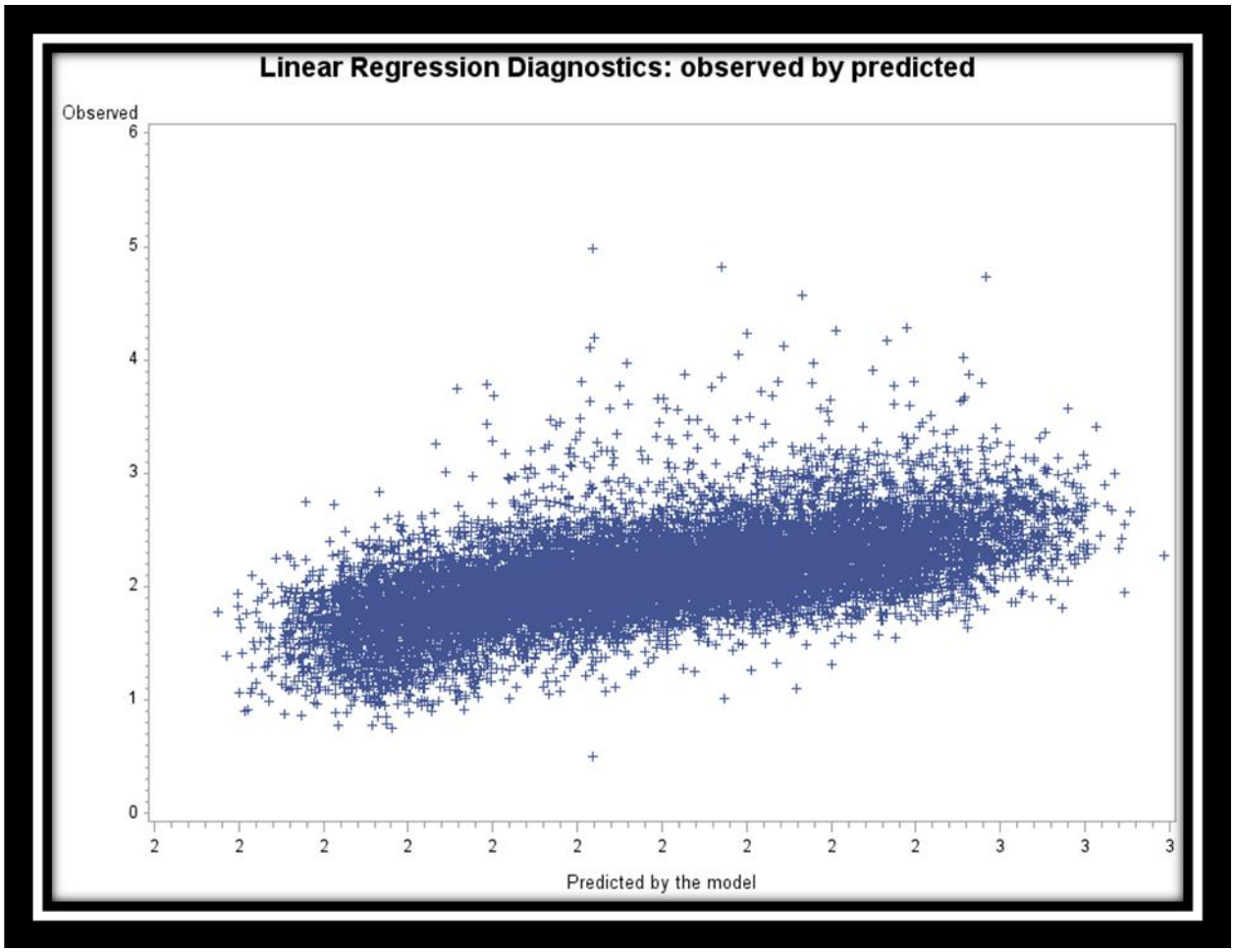

Figure 6. Linear regression model for log homocysteine, by serum cotinine category**.**

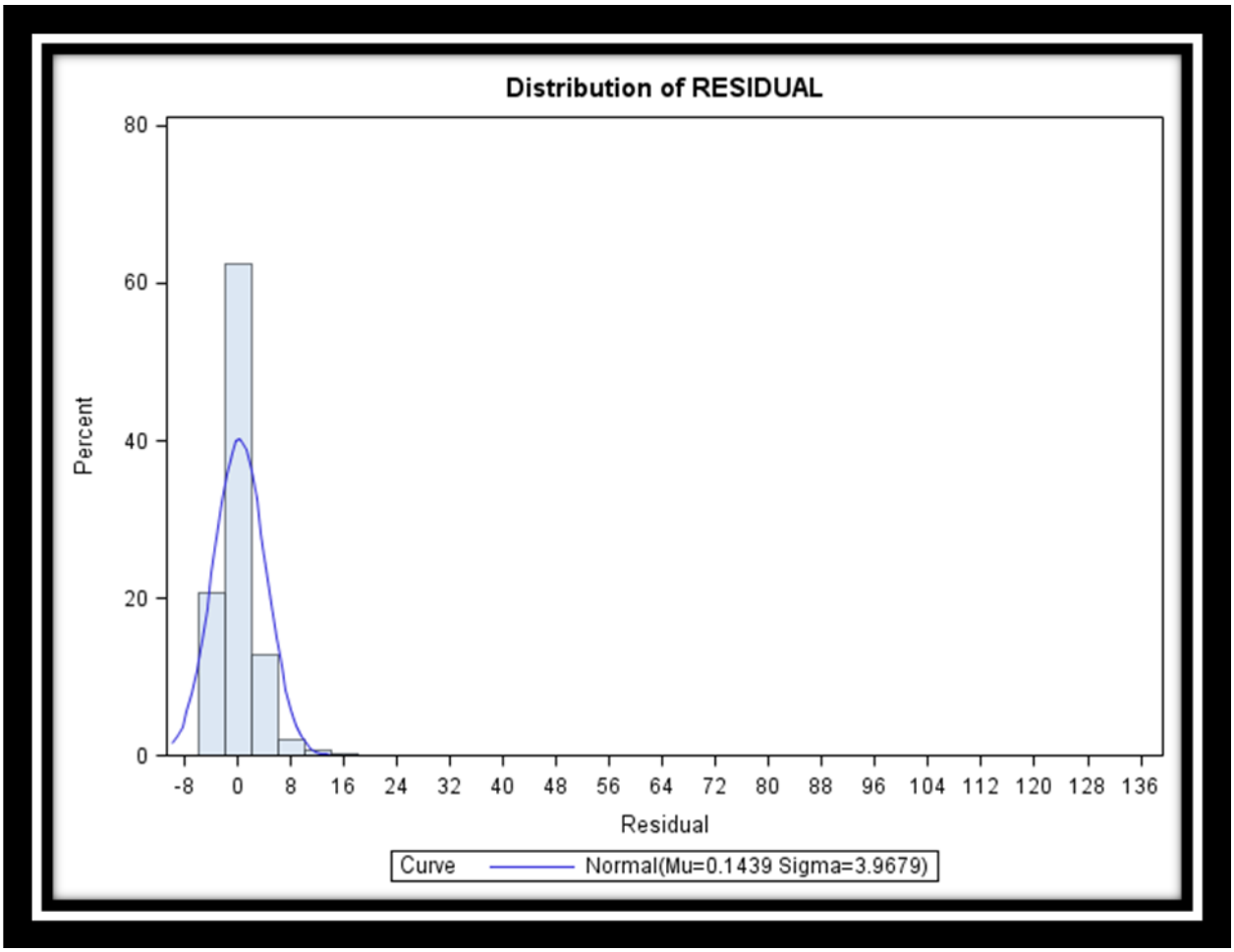

Figure 7. Linear regression model for homocysteine, by ETS exposure status at home and workplace.

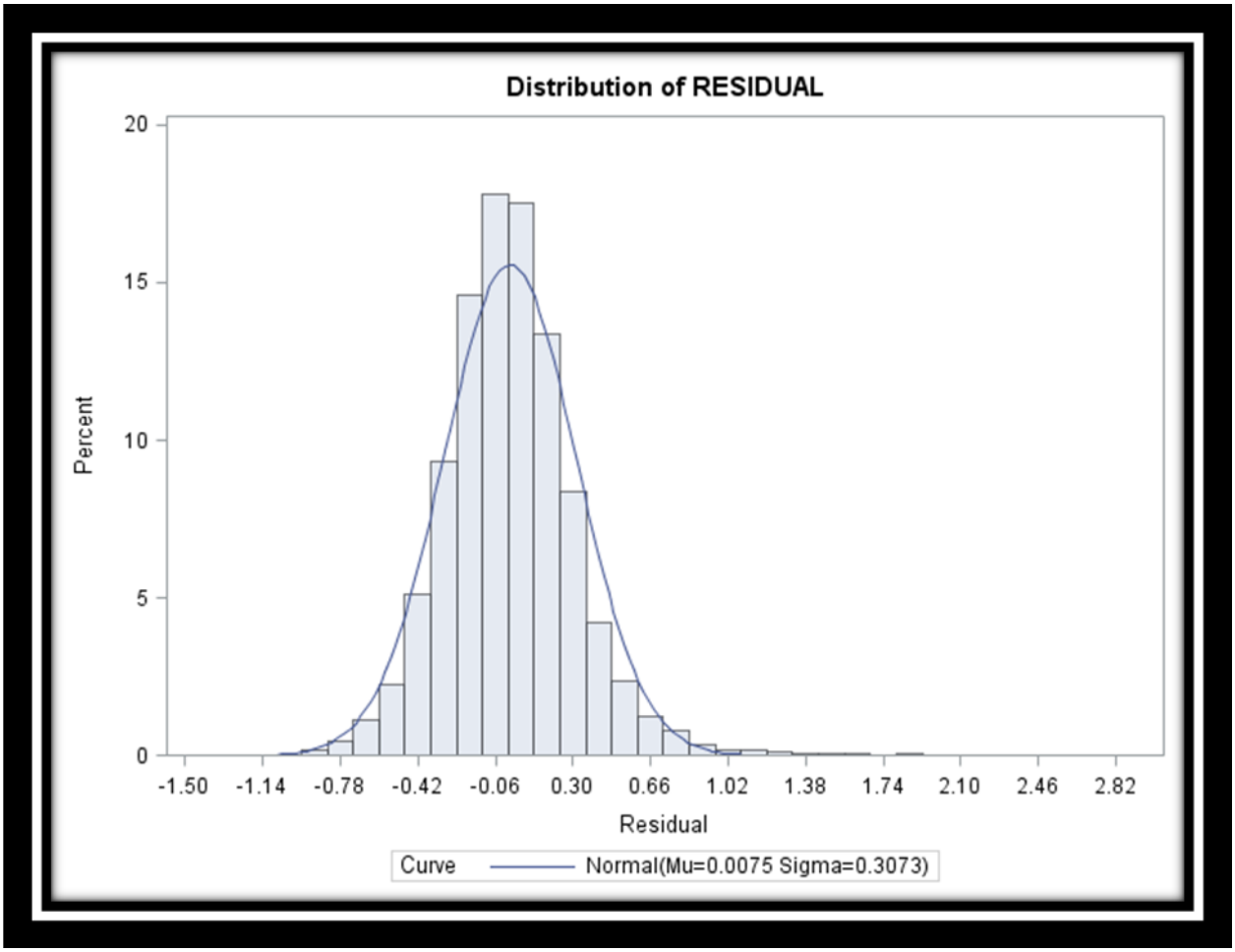

Figure 8. Linear regression model for log homocysteine, by ETS exposure status at home and workplace.

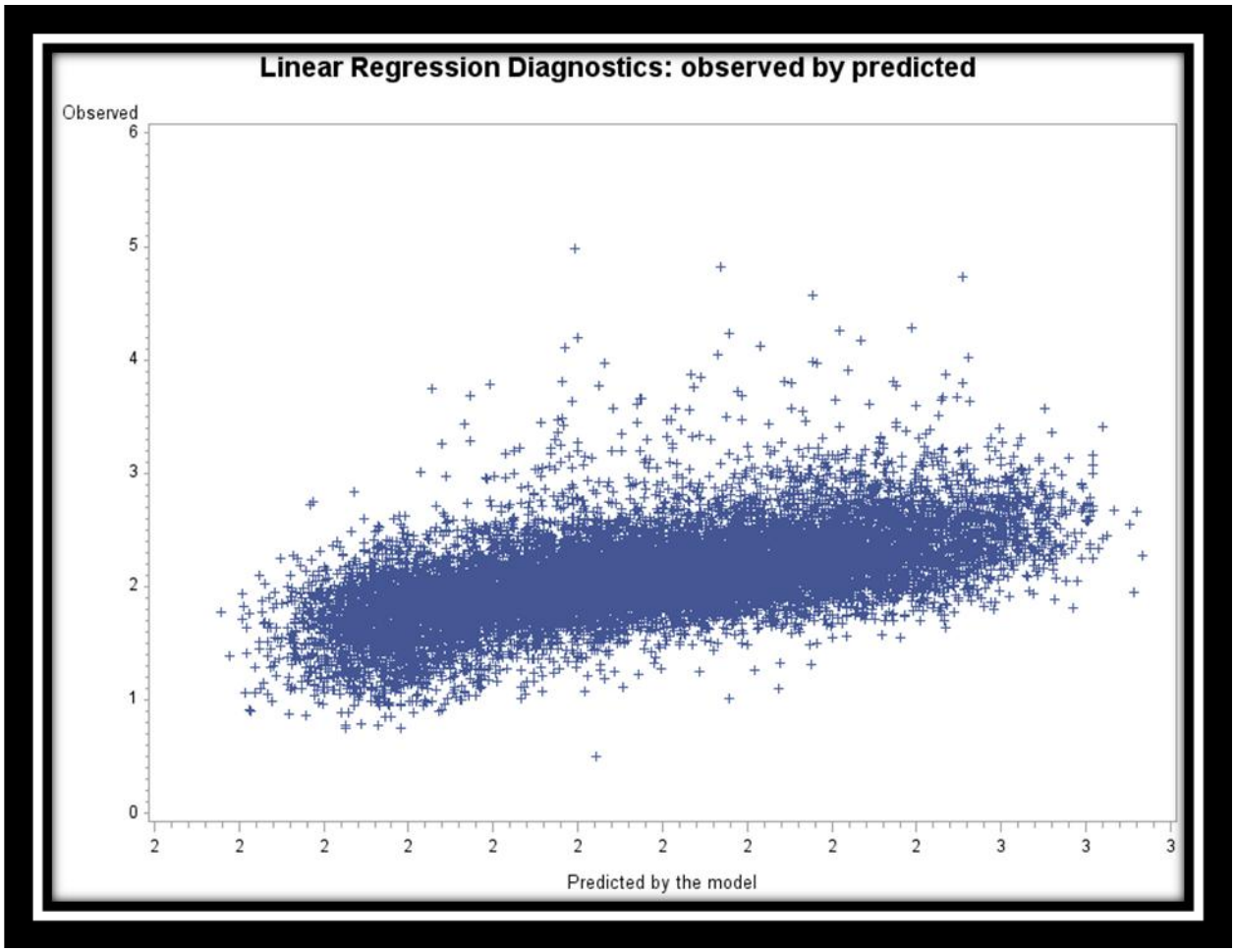

Figure 9. Linear regression model for log homocysteine, by ETS exposure status at home and workplace**.**

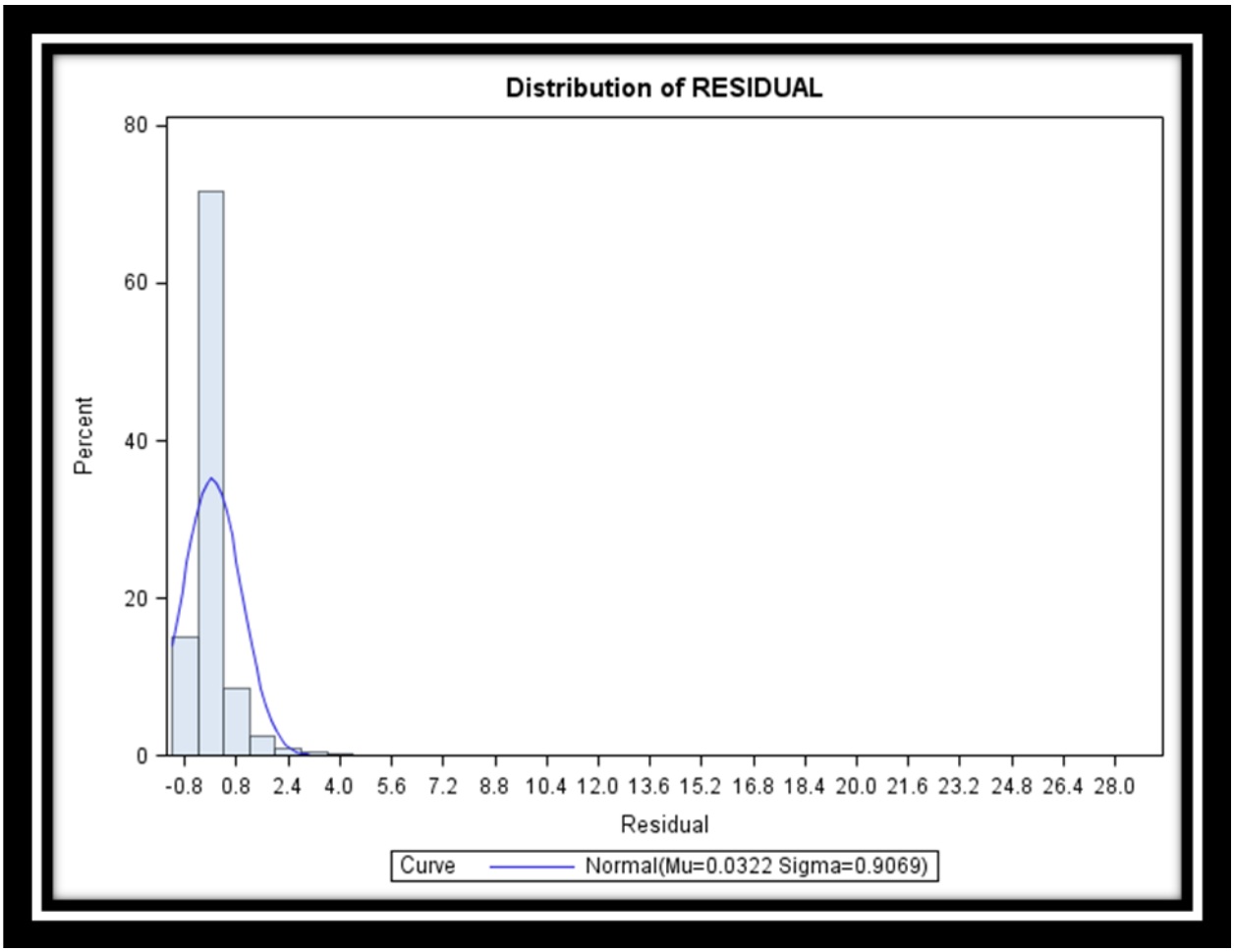

Figure 10. Linear regression model for c-reactive protein by ETS exposure status at home

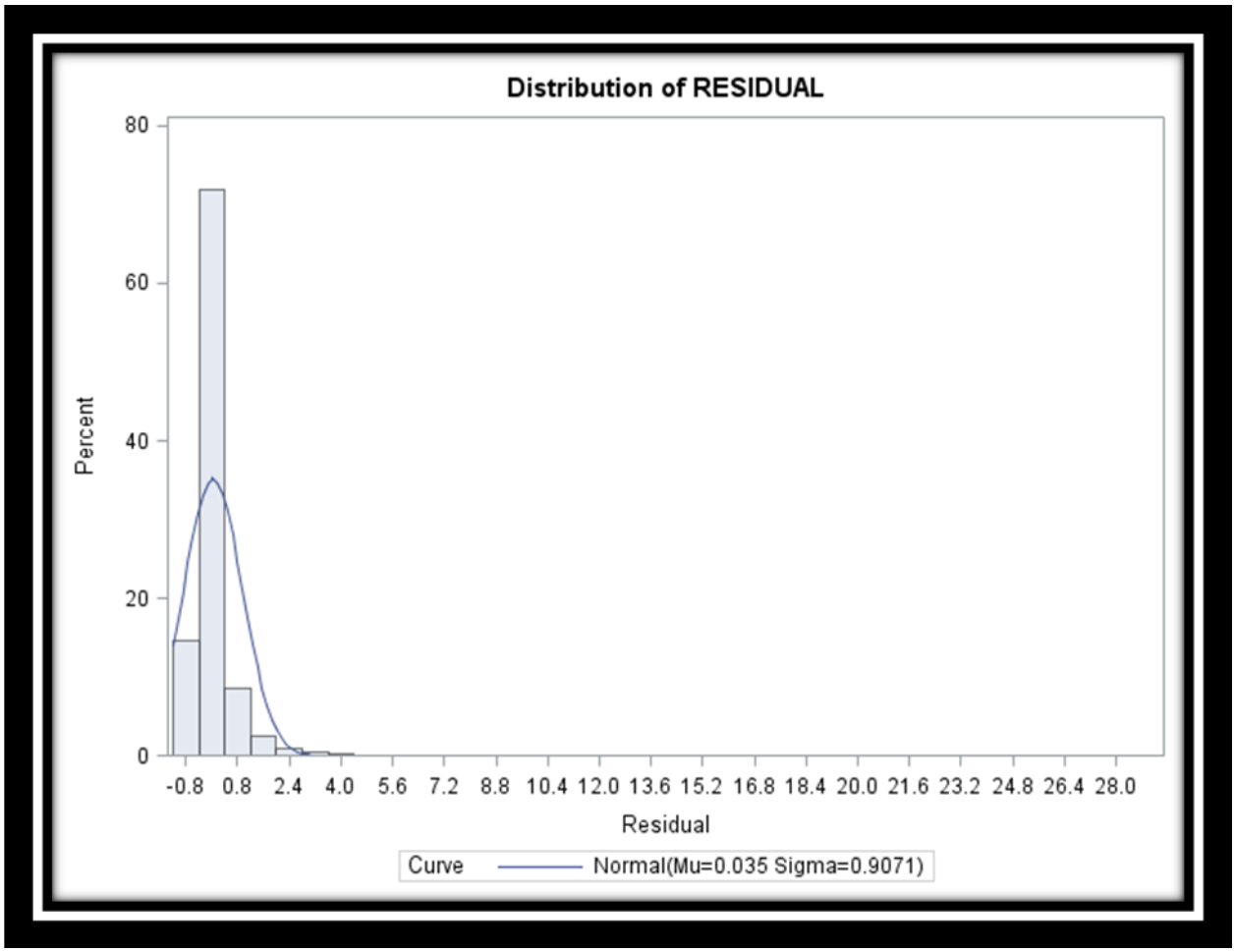

Figure 11. Linear regression model for c-reactive protein by ETS exposure status at home and workplace

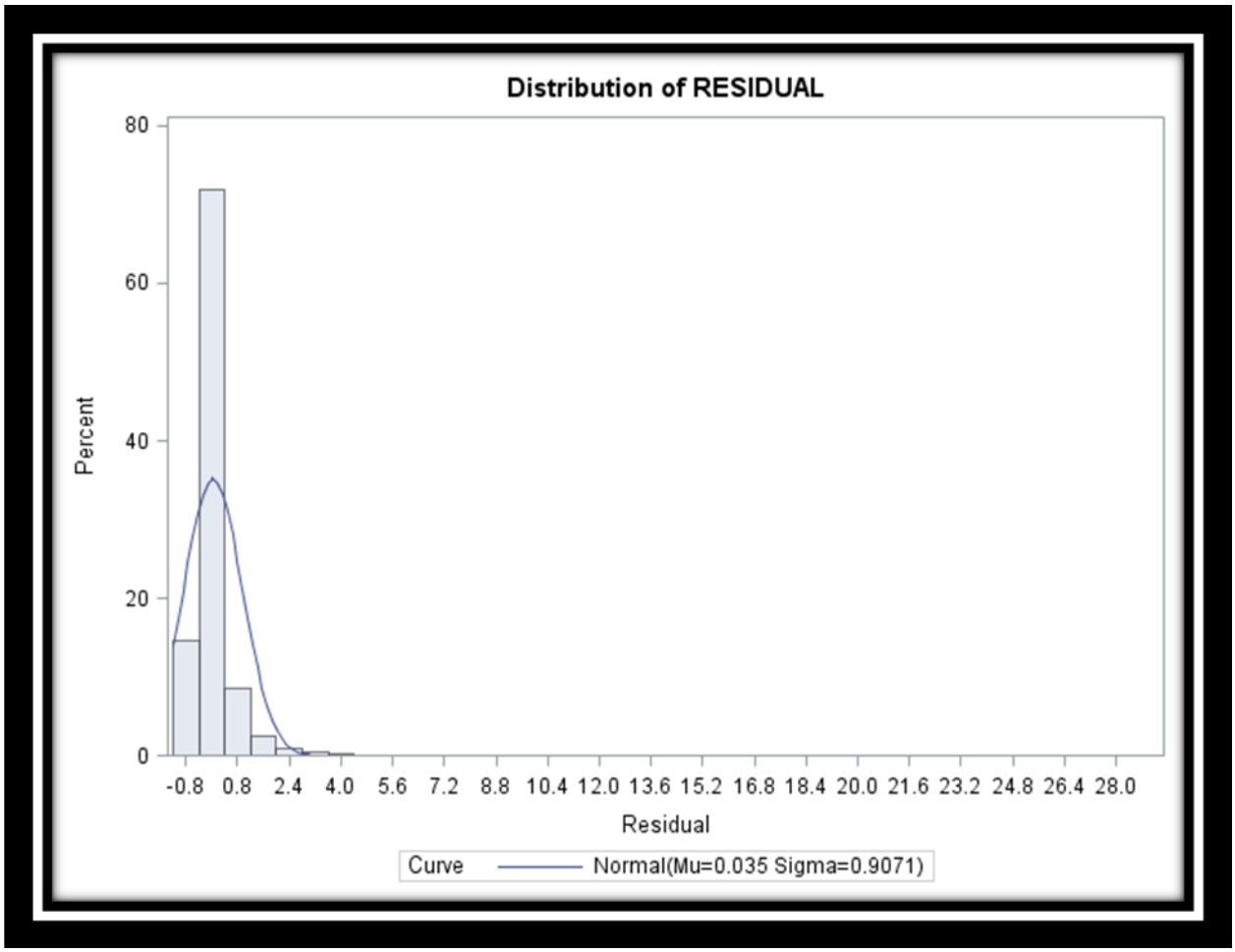

Figure 12. Linear regression model for c-reactive protein by ETS exposure status at home and workplace

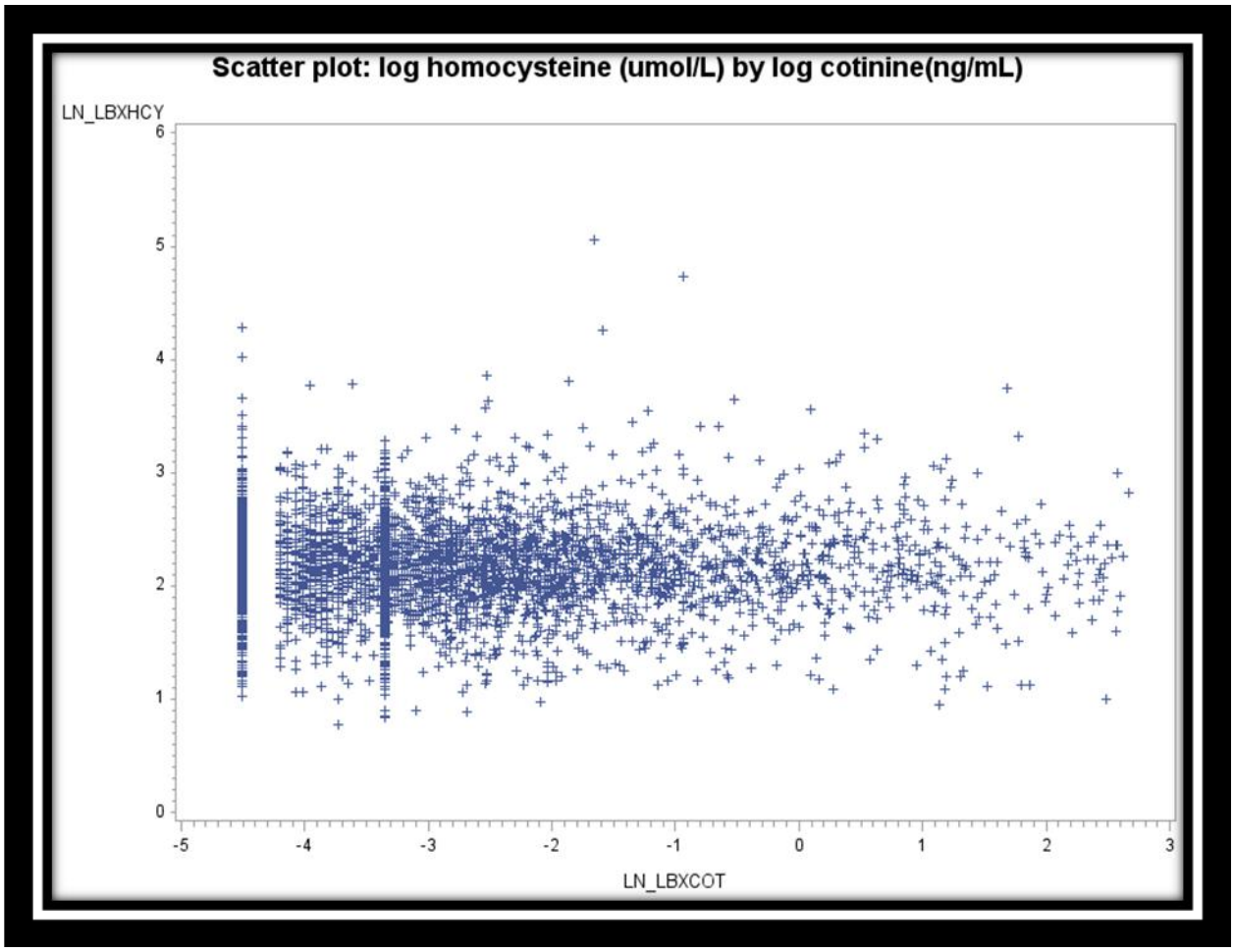

Figure 13. Scatter plot: log homocysteine by log cotinine

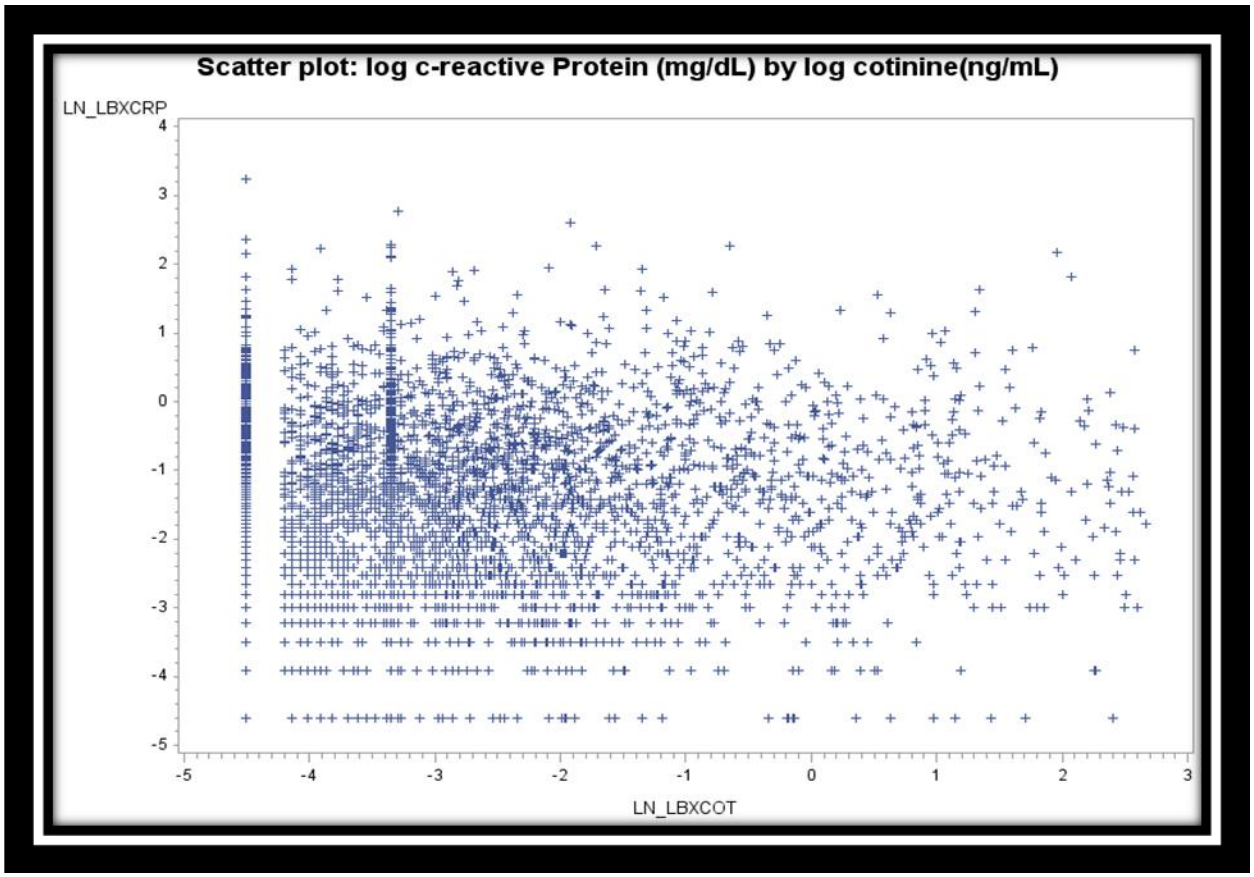

Figure 14. Scatter plot c-reactive protein by log cotinine