Exhaled Carbon Monoxide Level and Smoking Status in Urban Khon Kaen Adults

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Background: *Recent data has shown that a great number of Thai adults as well as people worldwide have died from smoking-related diseases. Measurements of exhaled carbon monoxide have been increasingly used to evaluate smoking status and cutoff levels of exhaled carbon monoxide and have been widely reported among other populations but not for the Thai people.*
Objective: *The purpose of the present research was to study the proper cutoff level for exhaled carbon monoxide for detecting smoking status among urban Thai adults residing in Khon Kaen province, Thailand as well as to study the effect of baseline characteristics in modifying the cutoff level of exhaled carbon monoxide.*
Study Design: *Cross-sectional analytic study.*
Material and Method: *The present study employed existing data whereby the study subjects comprised a total of 420 Thai adults, aged 15-70 years, residing in urban Khon Kaen province, Thailand during the year 2006. The data was obtained through interview and exhaled carbon monoxide measurement. The analyses employed descriptive, bivariate, and multivariable logistic regression.*
Results: *Findings from the final multivariable logistic regression model revealed good relation between exhaled carbon monoxide levels and tobacco smoking status. Other variables in the model included age-group and the interaction between exhaled carbon monoxide and age-group. Further analysis showed a greater odds ratio in the older age-group, with the odds ratios (95% CI) being 2.50 (1.87, 3.34) and 1.46 (1.31, 1.63) in the older (41-70 years) and younger (15-40 years) age-groups, respectively. In addition, proper cutoff of exhaled carbon monoxide for the older age-group was suggested as 7 ppm, while 8 ppm was more appropriate for the younger age-group. Based on the findings, a baseline characteristic for age modified cutoff level of carbon monoxide was established.*
Conclusion: *Differences in baseline characteristics should be considered in evaluating smoking status when choosing the cutoff level of exhaled carbon monoxide for any population.*

Keywords: *Exhaled carbon monoxide, Tobacco smoking, Baseline characteristic, Age*

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At least five million smokers worldwide and 52,000 Thai people die annually from smoking-related diseases[1]. Primarily, assessment of smoking status is often based on questionnaire. Until recently, measurements of exhaled carbon monoxide level have been used to increase the validity of smoking investigation due to the fact that the measurement of exhaled carbon monoxide level is simple to use, non-invasive, cheap, and portable. Moreover, this method can provide an immediate assessment of smoking status. It has been reported that the use of carbon monoxide monitor to demonstrate an immediate and potentially harmful consequence of smoking resulted in an increased number of people who complied with advice to quit smoking[2-5]. A number of studies have suggested different cutoff levels for exhaled carbon monoxide in detecting smoking status[4-12], and the possibility that exhaled carbon monoxide cutoff may vary according to different populations was once proposed[13].

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The relationship between exhaled carbon monoxide level and smoking status has been reported elsewhere but not among the Thai people. Therefore, the first objective of this research was to study the proper cutoff level for exhaled carbon monoxide in detecting smoking status among urban Thai adults residing in Khon Kaen province, Thailand. Moreover, there is no evidence thus regarding the influence of important baseline characteristics including age or age-group, gender, income, education, or occupational status of the people in the present study with regard to their effect exhaled in detecting/determining smoking status. Therefore, the second objective aimed to study the effect of baseline characteristics and their impact in modifying cutoff level of exhaled carbon monoxide among this group of Thai people.

Material and Method

Four hundred and twenty people, aged 15-70 years (mean age = 38.3 years), who resided in the urban area of Khon Kaen province, Thailand during 2006 were included in the present study. After the participants were informed of the purposes of the study, they were interviewed about their health, smoking status as well as background characteristics by a well-trained interviewer. Then, their exhaled carbon monoxide was measured using a portable Micro CO Meter (Micro Medical Ltd, Kent, UK). All people were reassured that the results were confidential in order to encourage full cooperation. The research protocol was approved by the Ethics Committee for Human Research at Khon Kaen University, Khon Kaen, Thailand.

Interview

Assessment of baseline characteristics included age (year), gender (male/female), education (none & lower primary school/upper primary school/lower secondary school/upper secondary school/vocational school university degree), monthly income (baht), marital status (single/married/widow/divorced), occupational status (unemployed/agriculture/government service/industrial worker/business/others) and religions (Buddhist/others). People who reported existing respiratory disease or systemic disease of any kind were excluded from the analysis. Questions on smoking history categorized the healthy participants into smoker and nonsmoker groups. A smoker was defined as a person who has smoked at least one cigarette a day for a minimum of one year. A Non-smoker was defined as a person who had never smoked cigarettes in the past 10 years before the time of the interview.

Exhaled carbon monoxide measurement

Exhaled carbon monoxide level was measured using the Micro CO Meter (Micro Medical Ltd, Kent, England). The measurement of exhaled CO was done in an open-air environment. The subjects were asked to exhale completely, inhale fully, and then hold their breath for 15 sec before exhaling rapidly into a disposable mouthpiece. Ambient CO levels were recorded before each breath to make sure that during measurements of exhaled CO in every participant, ambient air concentrations of CO were at 0-2 ppm. Based on the present study protocol requiring that all participants hold their breath for 15 seconds, undue impact of ambient air was not expected. The standardized breath-hold time of 15 sec. was determined to be adequate for equilibrium to take place[7].

Statistical analysis

The data management and analysis were done using SPSS for Windows version 11.5. Results were expressed for descriptive, bivariate, and multivariable logistic regression analyses. The Mann-Whitney U test was used to detect difference in mean CO levels between smokers and non-smokers based on the skewed distribution of this variable while an independent t-test was used to test for mean difference for continuous variables with normal distribution. For all categorical variables, differences between proportions based on Chi-square test were assessed. A value of p less than 0.05 was considered statistically significant. Multivariable logistic regression was used to model the relationship between exhaled CO level and smoking status.

Validity of the exhaled CO measurement was determined at different cutoff levels (6,7,8,9, and 10 ppm) using sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive (LR+), likelihood ratio negative (LR-) and odds ratio (OR). The assessments were calculated for all participants as well as for the age-groups 15-40 and 41-70 years.

Results

Exhaled CO levels were assessed in 420 subjects - 310 males (73.8%) and 110 females (26.2%). Among these, 169 (40.2%) were healthy smokers and 251 (59.8%) were healthy non-smokers. Results from Table 1 showed that the mean exhaled CO level was 12.47 $\pm$ 9.28 ppm for healthy smokers and 3.07 $\pm$ 2.69 ppm for healthy non-smokers. The mean exhaled CO level was significantly higher among healthy smokers compared to healthy non-smokers (p < 0.001; Mann-Whitney U test).

The bivariate relationships of CO level and baseline characteristics including age, age-group (which was categorized into 15-40 and 41-70 years to ensure adequacy of sample size in each group), monthly income, gender, marital status, education, occupation and religion, with smoking status are also shown in Table 1. Independent t-testing revealed a statistically significant difference for mean age between smokers and non-smokers. Smokers were younger compared to non-smokers (mean age 35.43 $\pm$ 15.02 for smokers and 40.31 $\pm$ 13.78 for non-smokers, p < 0.001; independent t-test). The major proportion of smokers (99.4%) were males (p < 0.001; Chi-square test), single male(51.5%, p < 0.001; Chi-square test) who worked in rice fields (53.1%, p = 0.012; chi-square test).

Table 2 displays findings from multivariable logistic regression analyses connecting smoking status (yes/no) to other variables. From this Table, all other social demographic variables were not related to smoking status and only exhaled CO, age-group, and

Table 1. CO level and baseline characteristics of non-smokers and smokers[a] (n = 420)

Variable	Tobacco smoking		p-value
	No (n = 251)	Yes (n = 169)	
CO level (mean $\pm$ SD in ppm)	3.07 $\pm$ 2.69	12.47 $\pm$ 9.28	<0.001[b]
Age (mean $\pm$ SD in year)	40.31 $\pm$ 13.78	35.43 $\pm$ 15.02	0.001[c]
Monthly income (mean $\pm$ SD in baht)	6573.00 $\pm$ 7362.00	5687.00 $\pm$ 4750.00	0.135
Age group			0.030[d]
15-40 years	129 (51.4%)	105 (62.1%)	
41-70 years	122 (48.6%)	64 (37.9%)	
Gender			<0.001[d]
Male	142 (56.6%)	168 (99.4%)	
Female	109 (43.4%)	1 (0.6%)	
Marital status			<0.001[d]
Single	59 (23.5%)	77 (45.6%)	
Married	172 (68.5%)	82 (48.5%)	
Widow	12 (4.8%)	2 (1.2%)	
Divorced	8 (3.2%)	8 (4.7%)	
Education			0.282
No education & Lower primary school	84 (33.5%)	47 (28.0%)	
Upper primary school	33 (13.1%)	23 (13.7%)	
Lower secondary school	18 (7.2%)	12 (7.1%)	
Upper secondary school	53 (21.1%)	29 (17.3%)	
Vocational school	17 (6.8%)	8 (4.8%)	
University degree & higher	46 (18.3%)	49 (29.2%)	
Occupational status			0. 012[d]
Unemployed	22 (8.8%)	4 (2.5%)	
Agriculture	100 (39.8%)	86 (53.1%)	
Government service	47 (18.7%)	27 (16.7%)	
Worker	47 (18.7%)	33 (20.4%)	
Business	25 (10.0%)	10 (6.2%)	
Others	10 (4.0%)	2 (1.2%)	
Religion			0.653
Buddhism	248 (98.8%)	3 (1.2%)	
Others	166 (98.2%)	3 (1.8%)	

[a] Total sample for some variables may not add up to 100 per cent due to incomplete data.
[b] Test of difference between mean ranks (Mann-Whitney U test), p < 0.05.
[c] Test of difference between means (Independent t-test), p < 0.05.
[d] Test of difference between proportions (Chi-square test), p < 0.05.

the interaction between the two variables were retained in the model with odds ratios at 95% confidence intervals shown in the Table. Based on the finding indicating that the interaction between exhaled CO and age-group was statistically significant, the relationship between smoking status and exhaled CO was assessed further for the younger (15-40 years) and older (41-70 years) age-groups.

Results in Table 3 confirmed that the age-group factor affected proper cutoff level of CO for detecting smoking status among this population. From this Table, an increased ratio of CO levels among older people (age-group 41-70 years) was found when compared to the younger age-group (15-40 years).

Table 4 provides definition of terms used in studying validity for measuring the exhaled CO including sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio positive (LR+), likelihood ratio negative (LR-) and odds ratio (OR). Sensitivity was defined as the ability of exhaled CO cutoff to detect smokers when smoking is present, which was calculated as "a/a+c." Specificity was the ability of exhaled CO cutoff to indicate a non-smoker when a non-smoker is present, which was measured as "d/b+d." Positive predictive value indicated the proportion of the subjects who were defined as smokers based on exhaled CO cutoff who were actually smokers, which was calculated as "a/a+b." Negative predictive value indicated the proportion of the subjects who were defined as non-smokers based on exhaled CO cutoff that were actually non-smokers, which was calculated as "d/c+d." Likelihood ratio positive (LR+) was the ratio of the sensitivity of a test to the false-positive error rate (alpha error rate), which was calculated as "[a/a+c] / [b/b+d]." Likelihood ratio negative (LR-) was the ratio of the false-negative error rate (beta error rate) to the specificity of a test, which was calculated as "[c/a+c] / [d/b+d]." Odds ratio (OR) represented the ratio of the likelihood ratio positive (LR+) to the likelihood ratio positive (LR+), which was simply calculated as "ad/bc." Therefore, the ratio of LR+/ LR- (or in other word the odds ratio) expressed the relationship between exhaled CO level and smoking status (the higher the odds ratio, the greater the correlation between exhaled CO level and smoking status).

Information regarding validity of different CO cutoff levels for all participants is shown in Table 5. From this Table, CO cutoff at levels 7, 8, and 9 were statistically significant ($p < 0.05$) in detecting smoking status. CO cutoff at 7 ppm was the optimal cutoff compared to the others based on sensitivity, specificity,

Table 2. Conditional odds ratio and 95% CI of variables associated with smoking status in the final multi-variable logistic regression model (n = 420)

Variables	95% confidence limit		
	Odds ratio	Lower	Upper
Exhaled carbon monoxide[a]	1.912	1.638	2.232
Age-group[b]	0.069	0.015	0.323
Interaction[c]	1.711	1.255	2.332

[a] Exhaled carbon monoxide is expressed as ppm
[b] Age-group is divided into 2 groups - 15-40 and 41-70 years
[c] The interaction is between exhaled carbon monoxide and age-group

Table 3. Conditional odds ratio and 95% CI of variables associated with smoking status in the final multi-variable logistic regression model

Age-group 15-40 years (n = 234)			
Variable	95% confidence limit		
	Odds ratio	Lower	Upper
Exhaled carbon monoxide	1.462	1.312	1.628
Age-group 41-70 Years (n = 186)			
	95% Confidence limit		
Variable	Odds ratio	Lower	Upper
Exhaled carbon monoxide	2.501	1.871	3.343

Table 4. Definition of terms used in validity test

Test	Gold standard		Total
	Positive	Negative	
Positive	a	b	a + b
Negative	c	d	c + d
Total	a + c	b + d	a + b + c + d

Sensitivity = a / a+c
Specificity = d / b+d
Positive predictive = a / a+b
Negative predictive = d / c+d
Likelihood ratio positive (LR+) = (a / a+c) / (b / b+d)
Likelihood ratio negative (LR-) = (c / a+c) / (d / b+d)
Odds ratio (OR) = ad / bc = LR+ / LR-

Table 5. Validity of different CO cutoff points for all participants (n = 420)

Test	CO6	CO7	CO8	CO9	CO10
ROC Curve*					
Area	0.567	0.771	0.780	0.740	0.676
Significant	0.379	0.001	<0.001	0.020	0.088
Sensitivity (%)	78.95	74.27	66.67	57.31	53.22
Specificity (%)	93.65	96.43	96.83	97.22	97.62
Positive predictive (%)	89.40	93.38	93.44	93.33	93.81
Negative predictive (%)	86.76	84.67	81.06	77.04	75.46
Likelihood ratio+ (LR+)	12.43	20.80	21.00	20.63	22.35
Likelihood ratio- (LR-)	0.22	0.27	0.34	0.44	0.48
Odds ratio (OR)	55.31	77.93	61.00	46.99	46.64

ROC Curve* H0: True area = 0.5

Table 6. Validity of different CO cutoff points for age group 15-40 years (n = 234)

Test	CO6	CO7	CO8	CO9	CO10
ROC Curve*					
Area	0.591	0.711	0.742	0.653	0.612
Significant	0.381	0.058	0.007	0.294	0.350
Sensitivity (%)	79.05	74.29	68.57	59.05	56.19
Specificity (%)	91.47	93.80	94.57	95.35	96.12
Positive predictive (%)	88.30	90.70	91.14	91.18	92.19
Negative predictive (%)	84.29	81.76	78.71	74.10	72.94
Likelihood ratio+ (LR+)	9.27	11.98	12.64	12.70	14.50
Likelihood ratio- (LR-)	0.23	0.27	0.33	0.43	0.46
Odds ratio (OR)	40.47	43.69	38.03	29.56	31.81

ROC Curve* H0: True area = 0.5

Table 7. Validity of different CO cutoff points for age group 41-70 years (n = 186)

Test	CO6	CO7	CO8	CO9	CO10
ROC Curve*					
Area	0.544	0.841	0.839	0.835	0.832
Significant	0.694	0.002	0.005	0.022	0.107
Sensitivity (%)	79.69	75.00	64.06	54.69	48.44
Specificity (%)	95.90	99.18	99.18	99.18	99.18
Positive predictive (%)	91.07	97.96	97.62	97.22	96.88
Negative predictive (%)	90.00	88.32	84.03	80.67	78.57
Likelihood ratio+ (LR+)	19.44	91.50	78.16	66.72	59.09
Likelihood ratio- (LR-)	0.21	0.25	0.36	0.46	0.52
Odds ratio (OR)	91.80	363.00	215.70	146.03	113.67

ROC Curve* H0: True area = 0.5

area under the ROC curve, predictive values, likelihood ratios and the highest odds ratio.

Results concerning the significance of the area under the ROC curve, together with sensitivity, specificity, predictive values, likelihood ratios, and odds ratios in Tables 6 and 7 supported the findings from previous studies suggesting that different cutoffs of exhaled CO should be selected for different age-groups.

For the people of age 15-40 years, CO 8 seemed to be better for detecting smoking status while CO 7 was the best cutoff to detect smoking status among people 41-70 years.

Discussion

The results from the present study have shown that exhaled CO levels may be used to distinguish smokers from non-smokers. In the present study, the exhaled CO levels were 3.07 $\pm$ 2.69 ppm in healthy non-smokers and 12.47 $\pm$ 9.28 ppm in healthy smokers. The exhaled CO level of 3.07 $\pm$ 2.69 ppm in healthy non-smokers was higher compared with other studies. In previous studies, exhaled CO levels were determined as 1.9 $\pm$ 0.9 ppm in Low et al[9] study, 1.5 $\pm$ 0.1 ppm in Zayasu et al[15] study, 1.2 $\pm$ 0.9 ppm in Yamaya et al[16] study, and 1.2 $\pm$ 0.3 ppm in Yamaya et al[17] study. However, this CO level was comparable to the CO level from the study of Hung et al (2006) in a study of exhaled carbon monoxide level in Taiwan whereby the exhaled CO level in healthy non-smokers was reported as 4.2 ppm (95% confidence interval 3.3-5.1 ppm)[5].

In addition, the exhaled CO level of 12.47 $\pm$ 9.28 ppm in healthy smokers was lower than the CO levels from other studies[6,7,15,16]. Middleton and Morice (2000) reported exhaled CO level of 17.4 $\pm$ 11.6 ppm[6] while Deveci et al (2004) reported the level of 17.13 $\pm$ 8.50 ppm in healthy smokers[7]. Zayasu et al (1997) reported exhaled CO of 21.6 $\pm$ 2.8 ppm[15] and Yamaya et al (1998) reported exhaled CO of 18.5 $\pm$ 2.5 ppm[16]. However, the exhaled CO of 12.47 $\pm$ 9.28 ppm in healthy smokers was comparable to 11.6 $\pm$ 6.2 ppm from the study of Low et al[9].

The finding that CO cutoff at 7 ppm was appropriate for detecting smoking status was comparable to some studies[8,14,19]. However, this cutoff was somewhat different from others[4,6,18,20,21]. Jarvis et al[4] reported that the optimal cutoff was 8 ppm (sensitivity 90%, selectivity 89%); Middleton and Morice[6] reported that the optimal cutoff was 6 ppm (selectivity 96%, sensitivity 94%); Crowley et al[18] also reported that a breath CO level greater than 8 ppm was strongly associated with self-reported smoking. Many studies used breath CO monitors at 10 ppm as the cutoff [20,21].

In conclusion, measurement of breath CO level can be used in confirming smoking status. In addition, an important baseline characteristic such as age can aid in establishing a proper CO cutoff for determining smoking status. Based on the significance of the area under the ROC curve, together with sensitivity, specificity, predictive value, likelihood ratio and odds ratio in the present study, an exhaled CO level of 7 ppm and higher suggested that a subject in the older ages study group is a smoker while a CO level of 8 ppm and higher was a more appropriate cutoff for younger people.

However, some limitations exist regarding omission of some factors that might influence the level of exhaled CO including the quantity of the cigarette or the type of tobacco that people smoke. Existing of a systemic disease other than respiratory diseases such as hemolytic anemia may also play a role in elevated exhaled CO level. Therefore, future studies of this kind should include those factors in the analysis.

In addition, the small sample size in the analysis limits external validity of the present study. Therefore, future studies should be conducted among a larger group of the population to increase generalizability of the study. Furthermore, the present study serves only cross-sectional baseline evidence for determining the relationship between exhaled CO and smoking status. Future intervention trials or follow-up studies should be conducted to make the best use of exhaled CO measurement in evaluating smoking status and motivating people to quit smoking.

Conflict of interest statement

None of the authors has a conflict of interest to declare in relation to this work.

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ระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกกับการสูบบุหรี่ในประชากรผู้ใหญ่เขตเมือง จังหวัดขอนแก่น

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ภูมิหลัง: *ประชากรไทยและประชากรโลกจำนวนมากเสียชีวิตจากโรคที่เกี่ยวข้องกับการสูบบุหรี่ การวัดระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกมีการนำมาใช้เพื่อประเมินสภาวะการสูบบุหรี่ โดยที่มีการรายงานจุดตัดที่ใช้แบ่งระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกเพื่อบอกสภาวะการสูบบุหรี่กันอย่างแพร่หลาย ในกลุ่มประชากรต่าง ๆ ทั่วโลกยกเว้นประชากรไทย*

วัตถุประสงค์: *การศึกษาครั้งนี้มีวัตถุประสงค์เพื่อศึกษา จุดตัดที่เหมาะสมเพื่อใช้แบ่งระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออก เพื่อบอกสภาวะการสูบบุหรี่ ในประชากรผู้ใหญ่ของจังหวัดขอนแก่น ประเทศไทย และศึกษาผลของตัวแปร หรือ ลักษณะพื้นฐานของประชากร ที่อาจมีผลต่อจุดตัดแบ่งที่เหมาะสม ของระดับก๊าซ คาร์บอนมอนอกไซด์ในลมหายใจออกดังกล่าว*

การออกแบบการศึกษา: *เป็นการศึกษาภาคตัดขวางเชิงวิเคราะห์*

วัสดุและวิธีการ: *การศึกษานี้วิเคราะห์ผลจากข้อมูลที่มีอยู่แล้ว โดยกลุ่มตัวอย่างประกอบด้วยผู้ใหญ่ชายและหญิงอายุ 15-70 ปี อาศัยอยู่ในเขตชานเมือง จังหวัดขอนแก่นในช่วงปี พ.ศ. 2549 จำนวน 420 คน วิธีการเก็บข้อมูลประกอบด้วย การสัมภาษณ์และวัดระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออก วิธีการวิเคราะห์ผลการศึกษากระทำโดยการพรรณนา การวิเคราะห์ความสัมพันธ์ระหว่างตัวแปรสองตัว และการวิเคราะห์ความสัมพันธ์หลายตัวแปรโดยใช้สมการถดถอยลอจิสติก*

ผลการศึกษา: *ผลการศึกษาจากสมการถดถอยลอจิสติก พบว่าสภาวะการสูบบุหรี่สัมพันธ์กับระดับก๊าซคาร์บอนมอนอกไซด์ ในลมหายใจออกโดยที่ตัวแปรกลุ่มอายุ และปฏิสัมพันธ์ ระหว่างกลุ่มอายุกับระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกปรากฏนัยสำคัญ ในแบบจำลองสมการถดถอยลอจิสติกนี้ด้วย เมื่อแบ่งการวิเคราะห์ตามกลุ่มอายุ พบว่ากลุ่มอายุมาก (41-70 ปี) มีอัตราส่วนความเสี่ยงและช่วงเชื่อมั่น 95% สูงกว่ากลุ่มอายุน้อย (15-40 ปี) โดยมีค่าอัตราส่วนความเสี่ยงและช่วงเชื่อมั่น 95% เท่ากับ 2.50 (1.87,3.34) และ 1.46 (1.31,1.63) ตามลำดับ นอกจากนี้ พบว่าจุดตัดแบ่งระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกที่เหมาะสมในกลุ่มอายุมาก คือ 7 ส่วนในล้านส่วน ขณะที่กลุ่มอายุน้อย เป็น 8 ส่วนในล้านส่วน*

สรุป: *ลักษณะพื้นฐานเช่นกลุ่มอายุมีผลต่อจุดตัดแบ่งที่เหมาะสม ของระดับก๊าซคาร์บอนมอนอกไซด์ ในลมหายใจออกในการศึกษาครั้งนี้ และถือเป็นข้อควรคำนึงในการเลือกจุดตัดแบ่งที่เหมาะสมของระดับก๊าซคาร์บอนมอนอกไซด์ในลมหายใจออกสำหรับกลุ่มประชากรอื่น ๆ ต่อไป*