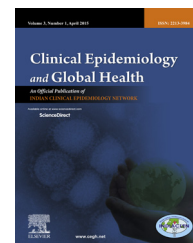


Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

journal homepage: [www.elsevier.com/locate/cegh](http://www.elsevier.com/locate/cegh)

## Original Article

# Outdoor air pollution improves the validity of a screening scale for cardiovascular disease (CVD) in clinical settings

Zeina Nasser<sup>a,b,\*</sup>, Pascale Salameh<sup>c</sup>, Elias Elias<sup>d</sup>, Habib Dakik<sup>e</sup>,  
Linda Abou Abbas<sup>a,b</sup>, Alain Levêque<sup>f</sup>

<sup>a</sup> PhD candidate in Public Health, School of Public Health, Free University of Brussels, Belgium Route de Lennik 808, CP 596, 1070 Brussels, Belgium

<sup>b</sup> Clinical and Epidemiological Research Laboratory (LCER), Doctoral School of Sciences and Technology, Lebanese University, Beirut 6573-14, Lebanon

<sup>c</sup> Clinical and Epidemiological Research Laboratory (LCER), Faculty of Pharmacy, Lebanese University, Beirut 6573-14, Lebanon

<sup>d</sup> Division of Neurosurgery, Department of Surgery, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon

<sup>e</sup> Division of Cardiology, Department of Internal Medicine, American University of Beirut, Riad El-Solh, Beirut 1107 2020, Lebanon

<sup>f</sup> Research Center in Epidemiology, Biostatistics and Clinical Research, School of Public Health, Free University of Brussels, Route de Lennik 808, CP 596, 1070, Brussels, Belgium

## ARTICLE INFO

## Article history:

Received 13 April 2015

Accepted 6 July 2015

Available online 29 July 2015

## Keywords:

Cardiovascular disease

Case-control

Outdoor air pollution

Screening

Prediction scale

## ABSTRACT

**Background:** Cardiovascular disease (CVD) is one of the leading causes of demises reported in the 21st century.

**Objective:** Our objective is to develop a screening score to estimate the probability of cardiovascular events, stressing on the importance of including outdoor air pollution to improve the validity of the scale among the Lebanese adult population.

**Methods:** A case-control study was carried out between October 2011 and October 2012 comparing CVD cases to a control group (Sample 1). Two multivariate analyses using logistic regression were carried out to evaluate predictors of the dependent variable. The second model included the outdoor air pollution variables, while the first did not. The adjusted odds ratios (OR) obtained were rounded to the nearest units and used as coefficients in the generated scales. Following the scale set up, a second case-control of 200 patients was also performed for clinical validation (Sample 2).

**Results:** Our study showed that the scale for screening of CVD, which included outdoor air pollution variables, can foresee the CVD outcomes better than the score using only the

\* Corresponding author at: Clinical and Epidemiological Research Laboratory (LCER), Doctoral School of Sciences and Technology, Lebanese University, Beirut, Lebanon. Tel.: +961 70 95 02 61; fax: +961 1 61 09 20.

E-mail address: [znasser@ulb.ac.be](mailto:znasser@ulb.ac.be) (Z. Nasser).

<http://dx.doi.org/10.1016/j.cegh.2015.07.002>

2213-3984/© 2015 INDIACLEN. Published by Elsevier, a division of Reed Elsevier India, Pvt. Ltd. All rights reserved.

traditional CVD risk factors. The areas under the curve were 0.737 (0.692–0.882;  $P < 0.001$ ) and 0.864 (0.825–0.903;  $P < 0.001$ ), respectively. Our results also provide some evidence of the clinical validity of the scale.

**Conclusion:** This screening scale could detect subjects at elevated risk for CVD in the clinical settings.

© 2015 INDIACLEN. Published by Elsevier, a division of Reed Elsevier India, Pvt. Ltd. All rights reserved.

## 1. Introduction

Cardiovascular disease (CVD) is one of the leading causes of demises reported in the 21st century.<sup>1</sup> It encases around 80% of the death rate of CVD in the developing countries.<sup>2</sup> Reasons attributed to its associated mortality include meagerly or ill-distributed health care services and curative instead of preventive medical care, which is mostly based in well-equipped expensive hospitals reached only by a handful ratio of the population.<sup>3</sup>

Risk factors of CVDs were assessed using multiple scores in an attempt to identify the persons at highest risk for developing CVD. The most eminent one is Framingham Risk Score (FRS), considered the backbone of several international clinical guidelines.<sup>4–7</sup> Other risk scores, such as Systematic Coronary Risk Evaluation (SCORE), Cardiovascular Risk Assessment in Italy (CUORE), Prospective Cardiovascular Munster (PROCAM), Assessing cardiovascular risk using the Scottish Intercollegiate Guidelines Network (AS-SIGN), CVD risk score (QRISK) for the United Kingdom, Reynolds Risk Score, and the National Health and Nutrition Examination Survey (NHANES), have been established in order to manage and reduce the burden of CVDs in the developed world.<sup>8–14</sup> These assessment tools include mainly age, gender, systolic blood pressure (SBP), smoking status, diabetes mellitus, lipid values, or family history as risk factors for CVD prediction.<sup>6,8–10</sup> Unfortunately, the aforementioned scores have not been validated in developing countries.

To our knowledge, an international risk score, which predicts 10 years risk of CVD, such as Framingham score, is not validated among Lebanese population. Lebanon, a small developing country in the Middle East, suffered from unstable political situation and limited resources to conduct such prospective cohort studies. Validating such screening tools would be helpful in minimal cost preventive efforts for identifying high-risk subjects in these countries, a place where limited screening resources exist.<sup>15,16</sup> Moreover, although outdoor air pollution has been acknowledged lately as an additional risk factor for CVD in developed and developing countries,<sup>17–25</sup> it was not included in any of the abovementioned scales. Nevertheless, we previously demonstrated that living near a busy highway and close to a local diesel generator were associated with CVD.<sup>26</sup> Thus, our aim in this study is to develop a score that can be used as a screening tool in clinical and epidemiological settings, stressing on the importance of adding outdoor air pollution to improve the validity of the scale among the Lebanese adult population.

## 2. Material and methods

### 2.1. Study design and population

This study was conducted in two phases: the factor structure of the screening scale was initially tested using a case–control study comparing CVD cases to a control group in six Lebanese hospitals between October 2011 and October 2012 (Sample 1). Following the score set-up, another case–control sample of 200 patients was also recruited for clinical validation (Sample 2). In both studies, inclusion criteria were defined as patients aged 40 years or above, hospitalized for CVD, diagnosed with ST/non-ST elevation myocardial infarction, and stable/unstable angina or heart failure, confirmed by a cardiologist based on their clinical presentation and laboratory exams.<sup>27</sup> The control group included any subject aged 40 years or above hospitalized for reasons excluding diabetes, hypertension, dyslipidemia, respiratory problems, or CVD. There were no significant differences in terms of age and gender between the two groups with  $P$  value  $>0.05$  in both samples.

### 2.2. Data collection

Subjects were interviewed by an independent assistant, after obtaining the informed consent. The ethical committee of our university waived the need for an official approval due to the observational nature of this study. We collected baseline data based on socio-demographic variables such as age, gender (male/female), smoking status (current/never), and family history of CVD. Hospital charts were used to collect variables such as SBP, triglyceride, high-density lipoprotein (HDL) concentration and low-density lipoprotein (LDL) concentration. Regarding the outdoor air pollution matter, we published a recent study conducted in Lebanon revealing that outdoor air pollution such as living near busy highway ( $<100$  m,  $>100$  m) and living close to a local diesel generator (No/Yes) was significantly associated with CVD.<sup>26</sup>

### 2.3. Statistical analysis

SPSS IBM version 22.0 was used to enter and analyze the data. In Sample 1, the dependent variable was disease-related variable, such as being diagnosed with CVD or not. Independent variables were cigarette smoking, HDL (yes/no), LDL (yes/no), SBP (yes/no), class age (40–65/ $>65$ ), family history of CVD (yes/no), and exposure to outdoor pollutants, which was assessed using the questions such as (Are you living near a busy highway  $<100$  m,  $>100$  meter?) and (Are you living close to local diesel generator?). Two multivariate analyses using

logistic regression were carried out to evaluate predictors of the dependent variable. The second model included the outdoor air pollution variables, while the first did not. Adjusted odds ratios (OR) and their 95% confidence intervals were reported. The Hosmer and Lemeshow goodness-of-fit was also calculated to assess the model fitting to data. The regressions of predictors served to generate two screening scales for CVD; the adjusted OR obtained were rounded to the nearest units and used as coefficients in the generated scales.

Thus, we compared two risks screening models, the first composed of the following risk factors (Score 1): class age (40–65/>65), gender (Male/Female), SBP (yes/no), smoking status (current/never), triglyceride (yes/no), HDL (yes/no), LDL (yes/no), and family history of CVD (yes/no). In the second model, we used the same risk factors of (Score 1) in addition to risk factors related to outdoor pollution derived from the previous study (living near a busy highway and living close to local diesel generator)<sup>26</sup> (Score 2). The calculated scores were applied for validation.

Receiver-operator characteristic (ROC) curves based on the logistic regression models were used to measure the discrimination of a prediction. The predictive discrimination of the two models was evaluated across several characteristics: sensibility (Se) and specificity (Sp), in addition to positive and negative predictive values (PPV and NPV, respectively). We also calculated the Kappa coefficient to assess concordance between physician's diagnosed cardiovascular event and that of CVD-screening score. The validity of the score was also

tested by comparing the means of CVD patients to those of control patients (Sample 2), using the corrected student t-test for means comparison.

### 3. Results

#### 3.1. Construction of the scales (Model 1 and Model 2)

The baseline characteristics of our study population are listed in Table 1. First sample analysis included 340 patients: 219 (64.4%) controls and 121 (35.6%) cases. The means of the risk factors (hypertension, triglycerides, and LDL) were significantly higher among cases than controls.

Table 2 shows two logistic regressions models predicting CVD in this case-control study. Taking into account the adjusted OR and rounding to the nearest unit, Two different scores were computed as follows: Score 1 = Class age\*2 + cigarette smoker\*2 + triglyceride\*5 + LDL\*5 + SBP\*3 + HDL and Score 2 = Class age\*2 + cigarette smoker\*2 + triglyceride\*6 + LDL\*5 + SBP\*3 + HDL + living near highway\*2 + living close to a local power plant\*3. The Hosmer and Lemeshow goodness-of-fit for both models suggest good calibration as 0.64 and 0.94, respectively. The first score has a minimum of 2 and maximum of 20 and second score has a minimum of 2 and maximum of 26. In the first model, the mean of CVD individuals was 13.26 and its standard deviation is 3.40, while in healthy controls, the mean was 7.83 and the standard deviation was 4.1 ( $P < 0.001$ ). In

**Table 1 – Risk factor profile of the participants in the case-control study.**

Characteristics	Controls n = 219 (64.4%)	Cases n = 121 (35.6%)	P value
Age years (Mean ± SD)	59.94 ± 14.53	62.94 ± 13.05	0.06
Gender			0.902
Male	116 (53.0)	63 (52.5)	
Female	103 (47.0)	58 (47.5)	
Current cigarette smoker			<0.001*
No	137 (63.1)	57 (47.1)	
Yes	80 (36.9)	64 (52.9)	
Family history of CVD <sup>a</sup>			0.02*
No	143 (65.9)	62 (51.7)	
Yes	74 (34.1)	58 (48.3)	
SBP, <sup>b</sup> mm/Hg (Mean ± SD)	122.5 ± 15.0	129.9 ± 19.1	<0.001*
Triglycerides, mmol/L (Mean ± SD)	1.65 ± 0.49	2.28 ± 0.75	<0.001*
HDL, <sup>c</sup> mmol/L (Mean ± SD)	1.33 ± 0.40	1.12 ± 0.36	<0.001*
LDL, <sup>d</sup> mmol/L (Mean ± SD)	2.23 ± 1.20	3.33 ± 0.99	<0.001*
Highway proximity <sup>e</sup>			0.001*
<100 m	128 (58.4)	47 (38.8)	
>100 m	91 (41.6)	74 (61.2)	
Local diesel generator proximity <sup>f</sup>			<0.001*
No	166 (75.8)	61 (50.4)	
Yes	53 (24.2)	60 (49.6)	

(Mean ± SD), Mean ± Standard deviation.

\* P value <0.005.

<sup>a</sup> Family history of cardiovascular diseases.

<sup>b</sup> Systolic Blood Pressure.

<sup>c</sup> High-density lipoprotein concentration.

<sup>d</sup> Low-density lipoprotein concentration.

<sup>e</sup> Are you living near a busy highway?

<sup>f</sup> Are you living close to local diesel generator?

**Table 2 – Logistic regression for predicting of cardiovascular disease events among the participants. Model 1 = traditional risk factors (TRF) of CVD and Model 2 = TRF of CVD in addition to outdoor air pollution exposure assessment.**

	Model 1			Model 2		
	OR	95% CI	P value	OR	95% CI	P value
Class age	1.84	1.01–3.38	0.049*	2.19	1.13–4.24	0.020
SBP <sup>a</sup>	2.92	1.26–6.75	0.012*	3.25	1.33–7.97	0.010*
Triglycerides	5.18	2.71–9.88	<0.001*	5.85	2.95–11.63	<0.001*
HDL <sup>b</sup>	0.48	0.25–0.92	<0.027*	0.39	0.19–0.78	<0.001*
LDL <sup>c</sup>	4.79	2.49–9.24	<0.001*	5.02	2.47–10.18	<0.001*
Cigarette smoker	2.19	1.20–3.98	0.01*	2.41	1.43–5.97	0.007*
Highway proximity <sup>d</sup>				2.42	1.27–4.56	0.011*
Generator proximity <sup>e</sup>				2.92	1.22–4.81	0.003*

OR: adjusted Odds Ratio; CI: Confidence Interval.

\* P value <0.05.

<sup>a</sup> Systolic blood pressure.

<sup>b</sup> High-density lipoprotein concentration.

<sup>c</sup> Low-density lipoprotein concentration.

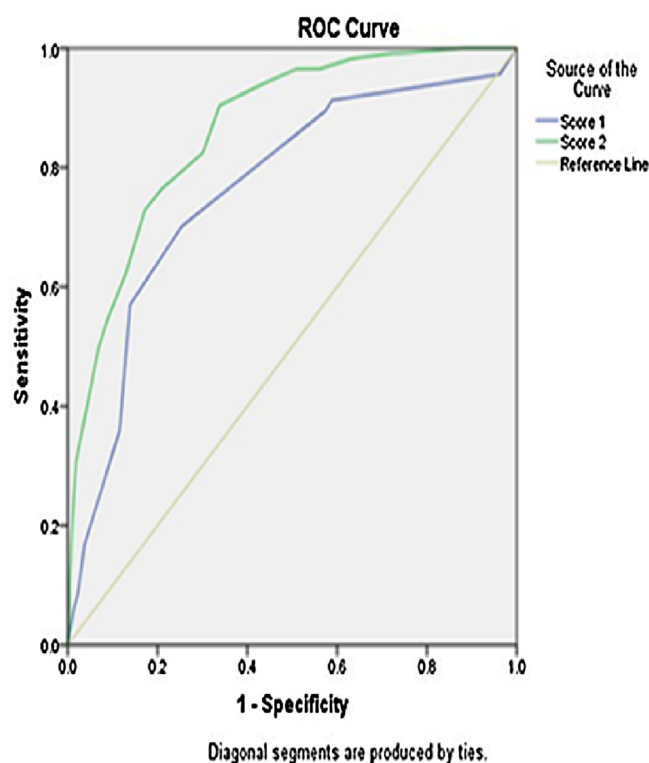
<sup>d</sup> Living near highway < 100 m.

<sup>e</sup> Living close to local diesel generator.

the second model, the mean of CVD individuals was 16.75 and its standard deviation was 3.98, while in healthy controls, the mean was 9.75 and the standard deviation was 4.66 ( $P < 0.001$ ).

### 3.2. Scales properties and thresholds

Receiver-operating characteristic (ROC) curves for CVD screening are shown in Fig. 1, comparing CVD patients with controls



**Fig. 1 – ROC curves for Score 1 and Score 2 to predict cardiovascular diseases. Abbreviation: ROC, receiver-operating characteristic curve.**

for the 2 scales. The areas under the curve were 0.737 (0.692–0.882;  $P < 0.001$ ) and 0.864 (0.825–0.903;  $P < 0.001$ ), respectively.

According to the ROC curve of the first scale (without outdoor air pollution; Fig. 1), the threshold that gave the best sensibility and specificity was 9.5: Se = 80% and Sp = 60%. After applying this threshold, we obtained a concordance between CVD-screening score and CVD patients confirmed by physician: Kappa = 0.412. Individuals with a positive score have a possibility of being a true CVD: OR = 2.81 [1.69–4.67]. In this situation, the PPV was 51% and the NPV was 84%.

According to the ROC curve of the second scale (with outdoor air pollution; Fig. 1), the threshold that gave the best sensibility and specificity was 11.5: Se = 90% and Sp = 66%. After applying this threshold, we obtained a good concordance between CVD-screening score and CVD patients confirmed by physician: Kappa = 0.601. Individuals with a positive score have a possibility of being a true CVD: OR = 5.34 [4.26–9.25]. In this situation, the PPV was 58% and the NPV was 92%.

### 3.3. Clinical validity

Results were clinically validated on a sample of 100 CVD patients. Their mean screening score was 16.95, with a standard deviation of 4.28 and with a statistical significant difference ( $P$  value 0.001). On the other hand, the 100 control patients had a mean screening score of 9.73 and a standard deviation of 4.28.

## 4. Discussion

We developed a new CVD risk assessment model, incorporating additional risk factors, such as living near highway and living close to a local diesel generator already recognized as CVD risk factor, for the Lebanese population.<sup>28</sup> Our study showed that the scale for screening of CVD, which included outdoor air pollution variables (Model 2), can predict the CVD outcomes better than the score using only the traditional CVD

risk factors (Model 1). This model was able to differentiate between patients at risk of CVD and healthy controls. Our values of predictive discrimination for the Model 2 were superior to the corresponding values in the Model 1. Moreover, the outdoor exposure risk factors significantly increased the C-statistic from 0.7 to 0.8. Clinical validity of the scale was also demonstrated through its ability to discriminate CVD patients from those who do not have CVD. Taken together, our findings provide some evidence in support of the fact that our generated scale is an appropriate tool for CVD screening.

Many measuring tools applied on large cohort population studies were developed to identify individuals at high-risk CVD.<sup>8–12,29</sup> However, we believe that this is the first work which includes outdoor air pollution risk factors for prediction of CVD events. We were able to formulate a tool for CVD screening with good diagnostic features in epidemiological or clinical settings; this tool would be mainly suitable for management of patients with CVD before special cardiovascular confirmatory test. This scale may help clinicians to pay attention to preventive measures of high-risk individuals rather than treating CVD events. Thus, this risk-screening model for CVDs can be used in the clinical settings. We also expect that in term of a screening tool used in public health settings, this scale could be applied to evaluate and stimulate much larger numbers of subjects to seek for help, particularly those who may not have regular checkups or lack the appropriate health care resources. The latter idea needs further validation in appropriate epidemiological settings.

The authors identified SBP, LDL, HDL, triglycerides, smoking, older age, and outdoor air pollution exposure as the significant variables associated with CVD in their logistic regression. These traditional risk factors were also found as significant variables in multiple established prediction scales, such as the FRS, PROCAM, CUORE, QRISK, and the Reynolds Risk Score.<sup>7,9,10,12,13</sup>

The case–control design of our study is not the perfect example in order to extrapolate the importance of the screening tool on our Lebanese population. However, it can be used as foundation for a future scale tested in longitudinal cohort studies. Furthermore, we should examine the performance of the screening scale using both internal and external validity measures to concur it to other international risk scores. Other limitations of the present study are the possibility of selection bias and information bias coupled with the questionnaire used.

## 5. Conclusion

In summary, our statistical model, containing risk factors, such as age, lipid profile, blood pressure, smoking status, and outdoor air pollution exposure allowed for screening of CVDs and can assist the cardiologist in decision making. This screening scale could detect persons at elevated risk for CVD in the clinical settings and may serve as an essential public health screening tool for the primary prevention of CVD, which is required to improve Lebanese cardiovascular health and decrease burden of public health cost.

## Conflicts of interest

The authors have none to declare.

## REFERENCES

- Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJL, eds. In: *Global Burden of Disease and Risk Factors*. Washington, DC: World Bank. The International Bank for Reconstruction and Development/The World Bank Group; 2006.
- Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349(9061):1269–1276.
- Maharani A, Tampubolon G. Unmet needs for cardiovascular care in Indonesia. *PLOS ONE*. 2014;9(8):e105831.
- Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J*. 1991;121(1 Pt 2):293–298.
- Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke*. 1991;22(3):312–318.
- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837–1847.
- D'Agostino Sr RB, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286(2):180–187.
- Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24(11):987–1003.
- Ferrario M, Chiodini P, Chambless LE, et al. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol*. 2005;34(2):413–421.
- Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Munster (PROCAM) study. *Circulation*. 2002;105(3):310–315.
- Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). *Heart (Br Cardiac Soc)*. 2007;93(2):172–176.
- Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. *BMJ (Clin Res Ed)*. 2007;335(7611):136.
- Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007;297(6):611–619.
- Gaziano TA, Young CR, Fitzmaurice G, Atwood S, Gaziano JM. Laboratory-based versus non-laboratory-based method for assessment of cardiovascular disease risk: the NHANES I Follow-up Study cohort. *Lancet*. 2008;371(9616):923–931.
- Bitton A, Gaziano TA. The Framingham Heart Study's impact on global risk assessment. *Prog Cardiovasc Dis*. 2010;53(1):68–78.
- Goff Jr DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report

- of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2935–2959.
17. Naddafi K, Hassanvand MS, Yunesian M, et al. Health impact assessment of air pollution in megacity of Tehran, Iran. *Iran J Environ Health Sci Eng*. 2012;9(1):28.
  18. Poursafa P, Kelishadi R, Lahijanzadeh A, et al. The relationship of air pollution and surrogate markers of endothelial dysfunction in a population-based sample of children. *BMC Public Health*. 2011;11:115.
  19. Sun H, Shamy M, Kluz T, et al. Gene expression profiling and pathway analysis of human bronchial epithelial cells exposed to airborne particulate matter collected from Saudi Arabia. *Toxicol Appl Pharmacol*. 2012;265(2):147–157.
  20. MacDonald Gibson J, Thomsen J, Launay F, Harder E, DeFelice N. Deaths and medical visits attributable to environmental pollution in the United Arab Emirates. *PLOS ONE*. 2013;8(3):e57536.
  21. Pope III CA, Burnett RT, Thun MJ, et al. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA*. 2002;287(9):1132–1141.
  22. Brook RD, Franklin B, Cascio W, et al. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation*. 2004;109(21):2655–2671.
  23. Brook RD, Rajagopalan S, Pope III CA et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121(21):2331–2378.
  24. Tonne C, Yanosky J, Gryparis A, et al. Traffic particles and occurrence of acute myocardial infarction: a case-control analysis. *Occup Environ Med*. 2009;66(12):797–804.
  25. Kunzli N, Jerrett M, Mack WJ, et al. Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect*. 2005;113(2):201–206.
  26. Nasser Z, Salameh P, Dakik H, Elias E, Abou Abbas L, Leveque A. Outdoor air pollution and cardiovascular diseases in Lebanon: a case-control study. *J Environ Public Health*. 2015;2015:810846.
  27. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388–416.
  28. Nasser Z, Salameh P, Dakik H, et al. Outdoor air pollution and cardiovascular diseases in Lebanon: a case-control study. *J Environ Public Health*. 2015;2015:6.
  29. Hippisley-Cox J, Coupland C, Vinogradova Y, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. *BMJ (Clin Res Ed)*. 2008;336(7659):1475–1482.