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Research Paper

The association of exhaled carbon monoxide with atrial fibrillation and left atrial size in the Framingham Heart Study

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ABSTRACT

Background: Exhaled carbon monoxide (eCO) is associated with subclinical and overt cardiovascular disease and stroke. The association between eCO with left atrial size, prevalent, or incident atrial fibrillation (AF) are uncertain.

Methods: eCO was measured using an Ecolyzer instrument among Framingham Heart Study Offspring and Omni participants who attended an examination from 1994 to 1998. We analyzed multivariable-adjusted (current smoking, and other covariates including age, race, sex, height, weight, systolic blood pressure, diastolic blood pressure, diabetes, hypertension treatment, prevalent myocardial infarction [MI], and prevalent heart failure [HF]). Cox and logistic regression models assessed the relations between eCO and incident AF (primary model), and prevalent AF and left atrial (LA) size (pre-specified secondary analyses). We also conducted secondary analyses adjusting for biomarkers, and interim MI and interim HF.

Results: Our study sample included 3814 participants (mean age 58 ± 10 years; 54.4 % women, 88.4 % White). During an average of 18.8 ± 6.5 years follow-up, 683 participants were diagnosed with AF. eCO was associated with incident AF after adjusting for established AF risk factors (HR, 1.31 [95 % CI, 1.09–1.58]). In secondary analyses the association remained significant after additionally adjusting for C-reactive protein and B-type natriuretic peptide, and interim MI and CHF, and in analyses excluding individuals who currently smoked. eCO was not significantly associated with LA size and prevalent AF.

Conclusion: In our community-based sample of individuals without AF, higher mean eCO concentrations were associated with incident AF. Further investigation is needed to explore the biological mechanisms linking eCO with AF.

1. Introduction

Exhaled CO (eCO) reflects both endogenous CO production and exogenous CO exposure, as it rapidly equilibrates across the alveolar-capillary membrane and exogenous CO from smoking and air pollution. Carbon monoxide (CO) is an endogenous byproduct of heme metabolism, which is cytoprotective at physiologic concentrations. At excess concentrations, CO impairs nitric oxide (NO)-mediated vasodilation, leads to the formation of reactive oxygen species, promotes adverse vascular remodeling, and fosters oxidative stress. [1–4]

Studies from the Framingham Heart Study (FHS) have reported that eCO was associated with traditional cardiovascular disease risk factors, the presence of metabolic syndrome, and subclinical cardiovascular disease. [5–7] Higher concentrations eCO were associated with higher risk of incident stroke, incident metabolic syndrome, and incident cardiovascular disease. [5,7,8]

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With the increasing incidence and prevalence of atrial fibrillation (AF), and its association with increased risk of stroke, dementia, myocardial infarction, heart failure, chronic kidney disease, and death; [9–17] we sought to assess the association between eCO and AF. We hypothesized that elevated eCO is associated with incident eCO and increased left atrial (LA) size. We sought to examine LA size as an intermediate phenotypic between eCO and the development of AF. In secondary analyses we examined additional intermediate factors potentially linking eCO to AF such as inflammatory or neurohormonal biomarkers.

2. Methods

2.1. Study sample

FHS is a longitudinal study that originally recruited adults living in Framingham, Massachusetts in 1948. In 1971 adult children of the Original cohort, along with spouses were recruited into the Offspring cohort. The Omni 1, a cohort of individuals from underrepresented racial and ethnic groups from the area were recruited in 1994. The design of the study and detailed information about these cohorts is published elsewhere. [18,19]

The study sample included 4038 FHS participants who participated in the Omni 1 Exam 1 (1994–1998) and Offspring Exam 6 (1995–1998). Participants were excluded for missing eCO measurements ($n = 52$), or missing covariates ($n = 57$). In the study of incident AF, participants with prevalent AF ($n = 115$) were also excluded. All study protocols used were approved by the Boston University Medical Center Institutional Review Board, and written informed consent was obtained from all participants.

2.2. Measuring exhaled carbon monoxide

Exhaled CO was measured at rest with the Ecolyzer (2000 series) instrument (Energetics Science Inc., Elmsford, NY), which uses an electrochemical sensor to quantify the level of CO gas in samples ranging from 1 to 100 ppm. The Ecolyzer instrument was calibrated to the midpoint of the scale each day using a canister of CO gas containing exactly $50_{ppm.}$ [6,8] Two readings were obtained from each participant and averaged, and the average Ecolyzer readings minus the base rate of the ambient CO level of the testing room constituted the eCO. For the present analyses, we censored exhaled CO levels >50 ppm and used the average of available eCO measurements from examination cycles 2 through 6 for each participant. The eCO measure is predominantly reflective of endogenous production of CO with minimal contamination by ambient exposure, as well as well as being reproducible. [1,6,8]

2.3. Covariates

We adjusted for age, sex, height, weight, current smoking, systolic blood pressure, diastolic blood pressure, diabetes, hypertension treatment, prevalent myocardial infarction, and prevalent heart failure as covariates based on the widely replicated CHARGE-AF model. [20,21]

Current cigarette smoking was considered present if the participant reported use the year before examination. Medications for blood pressure and diabetes mellitus were assessed by self-report. Weight was measured in kilograms and height in meters. Seated systolic and diastolic blood pressures were measured according to the FHS protocol. Diabetes was defined as treatment with a hypoglycemic agent, fasting blood glucose ≥126 mg/dL, or non-fasting glucose of ≥200 mg/dL. Myocardial infarction and heart failure were adjudicated by a panel of three physicians using written FHS criteria after reviewing FHS and all available outside medical records. [22,23]

High-sensitivity C-reactive protein (CRP) and B-type natriuretic peptide (BNP), were measured at the FHS clinic during the 6th examination cycle on fasting samples. [24] CRP was measured using a Dade Behring BN100 nephelometer, and plasma BNP was measured using high-sensitivity immunoradiometric assays (Shionogi, Japan).

2.4. Outcome events and echocardiographic measures

Participants were designated as having AF if an ECG at an FHS examination demonstrated atrial fibrillation or atrial flutter or if it was documented in the participants' outside medical records, interim hospitalizations, outside ECGs, or ambulatory ECG monitoring results. LA diameter was assessed using M-mode echocardiographic measurements obtained during the 6th FHS examination. [25]

3. Statistical analysis

Due to the skewness, the eCO levels were loge transformed and standardized. Descriptive statistics were reported as n (%), mean ± SD, or if skewed median [25th and 75th percentile]. We examined the association between eCO levels and incident AF using Cox proportional hazards models with robust sandwich estimators, to account for the relatedness of some participants.

Follow-up times were censored at the last follow-up time at the end of 2019 or death. The proportional hazards assumption was assessed using Schoenfeld residuals and the log minus log plots. All models were adjusted for age and sex. Our primary model was additionally adjusted for established risk factors associated with AF from the CHARGE-AF model, [20] described above. In addition, we used the Fine and Grey model to assess the competing risk of death given the extended follow-up. For display purposes, we created Kaplan-Meier curves based on eCO tertiles.

In the secondary analyses, we additionally adjusted for c-reactive protein and B-type natriuretic peptide. We also adjusted for both interim myocardial infarction and interim heart failure. We further tested for effect modification by age (≥65 and < 65 years old), sex (female vs male), and smoking status (current smoking vs never smoking or prior smoking). We also examined the association of eCO with LA size using the linear mixed effect model and the association of eCO with prevalent AF using generalized estimating equation models. Both models were adjusted for the same covariates as the primary model.

Statistical significance was considered a two-sided $P < 0.05$. All analyses were performed using the R software package version 4.0.3.

4. Results

In the primary analysis, we studied 3814 participants without prevalent AF. The mean age of the participants was 58 ± 10 years, 54.4 % were women, 88.4 % were White individuals, and 15.2 % currently smoked (Table 1). The median eCO was 8.2 ppm [ppm, 25th percentile 4.0 and 75th percentile 18.1]. During an average of 18.8 ± 6.5 years follow-up, 683 participants were diagnosed with AF. The clinical characteristics of participants with prevalent AF, incident AF, and AF-free at the index examination are shown in Table 1.

As displayed in Table 2, eCO was associated with incident AF after adjusting for established AF risk factors (HR, 1.31, 95 % confidence interval [CI], 1.09–1.58). Higher eCO levels were associated with increased cumulative risk of AF; as can be seen in Fig. 1 the risk of AF increased with higher tertiles of eCO.

The association remained significant after additionally adjusting for CRP and BNP, and interim myocardial infarction and heart failure (Table 2). With regards to the association between eCO and incident AF, we did not observe statistically significant interactions by age, sex, or smoking status (Table 3). In particular, eCO was associated with incident AF in analyses excluding individuals who currently smoked.

We further examined the association of eCO with LA size and prevalent AF. As shown in Supplemental Tables 2 and 3, eCO was not significantly associated with LA size or prevalent AF in either age- and sex-adjusted models or multivariable-adjusted models.

Table 1
Baseline characteristics of the study participants.

Variable	Participants without prevalent AF $n = 3814$
Age, years	58 ± 10
Women	2075 (54.4 %)
Race	
White	3372 (88.4 %)
Black	162 (4.2 %)
Asian	73 (1.9 %)
Other	207 (5.4 %)
Hispanic ethnicity	189 (5.0 %)
Height, cm	167 ± 10
Weight, kg	78 ± 17
Current smoking	578 (15.2 %)
Systolic blood pressure, mmHg	128 ± 19
Diastolic blood pressure, mmHg	75 ± 10
Antihypertensive medication use	1011 (26.5 %)
Diabetes mellitus	358 (9.4 %)
Prevalent myocardial infarction	122 (3.2 %)
Prevalent heart failure	24 (0.6 %)
Left atrium diameter (cm)	4.0 ± 0.5
CRP, mg/L, median [25 %, 75 %]	2.0 [0.9, 4.7]
BNP, pg/mL, median [25 %, 75 %]	8.2 [4.0, 18.1]
eCO, ppm, median [25 %, 75 %]	4.5 [3.8, 6.5]
Ln (eCO)	1.7 ± 0.6

Values are represented as n (%) for dichotomous variables or mean ± standard deviation (SD) for continuous variables or median [25th, 75th percentile] for skewed continuous variables.
All values for exhaled carbon monoxide (eCO) are the average values taken from examinations 2 through 6. CRP, C-reactive protein; BNP, B-type natriuretic peptide.

Table 2
Association of eCO with incident AF.

Adjustment	#Referents	Incident AF, n	HR	95 % CI	P
Age and sex	3131	683	1.35	1.18–1.54	<0.001
Multivariable*	3131	683	1.31	1.09-1.58	0.005
Multivariable, CRP, and BNP	2596	637	1.23	1.00–1.50	0.05
Multivariable, interim MI, and interim HF	3131	683	1.29	1.07–1.56	0.008
Multivariable* accounting for competing risk of death	3131	683	1.24	1.10–1.51	0.002

HR: Hazard ratio, expressed as one unit of $\log_e$ exhaled carbon monoxide (eCO); CI: confidence interval; *P*-values listed were not adjusted for multiple testing.
CRP, c-reactive protein; BNP, B-type natriuretic peptide, MI, myocardial infarction; HF, heart failure.
* Multivariable models included age, sex, smoking, height, weight, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes mellitus, prevalent myocardial infarction, and prevalent heart failure.

5. Discussion

In our community-based study, we observed that eCO was associated with incident AF accounting for standard risk factors. In secondary analyses eCO remained associated with incident AF further adjusting for inflammatory (CRP) and neurohormonal markers (BNP). The association between eCO and incident AF persisted accounting for interim myocardial infarction and heart failure, and for the competing risk of death. We did not observe significant effect modification in the relation between eCO and incident AF by age, sex, or smoking status. In the secondary models, eCO was not significantly associated with either LA size and prevalent AF.

Prior studies done by FHS reported eCO was associated with traditional cardiovascular disease risk factors, the presence of metabolic syndrome, and subclinical cardiovascular disease. [5–7] At higher concentrations, eCO was associated with higher risk of incident cardiovascular disease, metabolic syndrome, and stroke. [5,7,8] To our knowledge, no study has assessed the association between eCO and incident AF, left atrial size, or prevalent AF. This void in literature was well suited to be filled by the Framingham Heart Study (FHS), given the longitudinal routine ascertainment of events in the cohort.

The endogenous production of CO occurs through the constitutive and inducible action of heme oxygenase (2 and 1, respectively) during the catabolism of heme. [26] CO has cytoprotective and homeostatic functions, playing an important role in the human stress response, especially in the modulation of cellular antioxidant defense and vascular endothelial injury. [8,26–28] At higher levels, endogenous CO inhibits the action of endothelial nitric oxide, which is associated with prothrombogenic and pro-inflammatory states, and contributes to cardiometabolic disease by promoting oxidative stress. [1,4] In animal models, CO appears to be a modulator of cardiometabolic disease by promoting hypertension and endothelial dysfunction. [29]

Smoking and pollution are known exogenous contributors to eCO. The average eCO concentrations in individuals who smoke have been observed to be significantly higher than those who do not smoke, and in individuals who do not smoke, the average eCO is significantly higher in citizens residing in big cities than small towns, suggesting that consistent exposure to increased concentrations of air pollution and cigarette smoking affect concentrations of eCO. [30–34] CO concentrations, aside from their connections to cardiometabolic and vascular pathways, mirror the heme oxygenase activity involved in CO production during heme metabolism. [8,35] Heme oxygenase-1 is an increasingly acknowledged regulator of cardiovascular risk, showcasing notable cardioprotective effects through its modulation of cardiac inflammatory processes, cellular signaling, and mitochondrial function. [8,35,36]

Our study findings demonstrate the absence of a statistically significant association between eCO levels and LA size. Prior studies from FHS have shown a predictive link between LA size and the development of AF. [37–43] Consequently, our observation of an association between eCO and incident AF, without a concurrent association with LA size and prevalent AF, suggests that the relationship between eCO and incident AF was not driven by LA remodeling as a predisposing factor for AF development. [38,39,44–46]

The mechanistic pathways underlying our findings have several plausible explanations. It is possible that elevated eCO levels might influence the development of intermediate cardiovascular disease risk factors that contribute to the etiopathogenesis of AF, such as inflammation, neurohormonal dysregulation, and oxidative stress. [47] Alternatively, eCO may potentially serve as an indicator of subclinical disease burden, which in turn could predispose individuals to the development of AF. It is also possible that our results could be influenced by false positives or the presence of unaccounted confounding variables, possibly related to other environmental gases and pollutants that were not considered in our analytical framework. Subsequent studies are needed to assess the potential of eCO as a valuable clinical biomarker for predicting AF risk in specific populations, while exploring the role modulation of CO or heme oxygenase pathways may offer into reducing AF risk. [8]

6. Limitations and strengths

The quantification of exhaled carbon monoxide (CO) levels can be influenced by various factors related to both micro- and macro-environmental exposure to combustion byproducts. [7,48,49] In our study, we acknowledge that our data lacked reliable measurements pertaining to second-hand smoke exposure, occupational smoke exposure, or environmental influences, such as ambient air pollution. Furthermore, we did not possess individual- or regional-level data on contemporaneous atmospheric CO levels. [7,49]

Although current smoking status was ascertained through

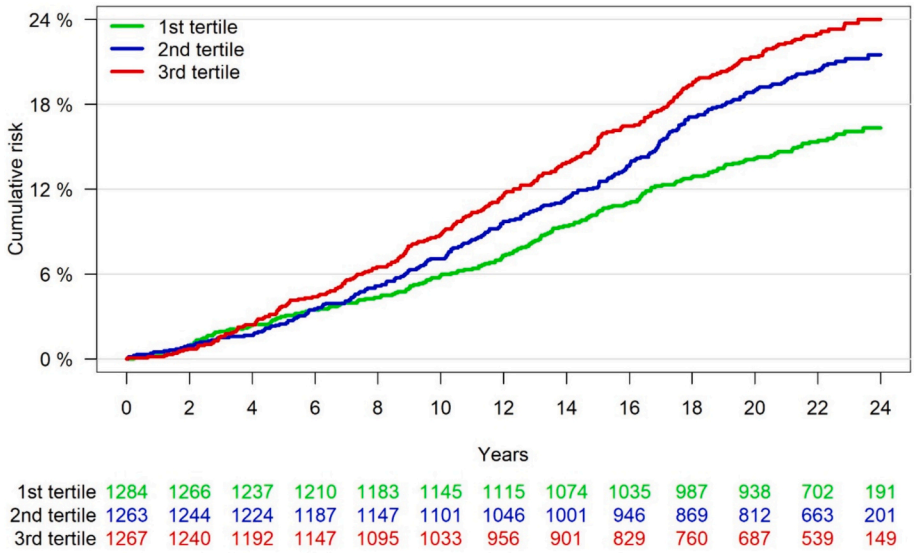

Fig. 1. Cumulative risk curve of AF association with eCO Participants were divided into three tertile groups based on their eCO levels. The lower panel shows the number of participants at risk during the study period.

Table 3
Association of eCO with incident AF in different subgroups.

Model*	HR	CI (95 %)	P	HR	CI (95 %)	P	P of interaction
Age-stratified	>60 years			≤60 years			0.72
	1.19	0.93–1.53	0.17	1.22	0.93–1.62	0.16	
Sex-stratified	Women			Men			0.45
	1.32	0.97–1.79	0.08	1.30	1.02–1.65	0.03	
Smoking-stratified	Current smoking			Never or previous smoking			0.34
	1.07	0.72–1.57	0.74	1.39	1.13–1.72	0.002	

Covariates include age (except for age-stratified model), sex (except for sex-stratified model), smoking (excepted for smoking stratified model), height, weight, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes mellitus, prevalent myocardial infarction, and prevalent heart failure.
HR: Hazard ratio, expressed as one unit of log(eCO); CI: confidence interval; P-values were not adjusted for multiple testing.

questionnaires, there remains a possibility of misclassification due to misreporting of current smoking, inaccuracies in prior smoking history, or the inability to account for secondhand smoke or for environmental pollutants, such as nitric oxides or sulfur oxides [8]. Ambient air pollution, known to contain CO and contribute to atherosclerotic vascular disease, presents a complex issue influenced by factors such as automobile type, proximity to major roadways, and home heating methods like kerosene stoves, further complicated by evolving trends indicating decreasing CO concentrations in ambient air in recent decades [49–53].

Hence, it is imperative to acknowledge that our analyses did not encompass a comprehensive assessment of CO exposure histories. To better address this issue, future epidemiological studies assessing stroke risk may consider the use of environmental or personal sensors to account for exogenous CO exposure and explore the role of other air pollutants in a more nuanced manner more comprehensively. Also, being an observational study, residual confounding cannot be fully excluded; hence causal relationships cannot be established. In addition, our prevalent AF analyses may have been underpowered. Left atrial measurements were made by M-mode echocardiogram and may have misclassified left atrial size.

Most participants were of European ancestry, from New England in the US, with ages ranging from middle to older-aged adults; the generalizability to other ages, regions, and other races and ethnicities is uncertain. There was also limited information about the types of AF (e.g., paroxysmal vs. persistent, etc.). We acknowledge that AF is frequently clinically unrecognized, and we undoubtedly failed to detect some incident AF. In addition, we assessed eCO at a single time point, which occurred in some cases many years prior to incident AF.

7. Conclusion

Our study observed an association between eCO and incident AF after adjusting for known AF-related risk factors. There is a need for more research to better understand how eCO may contribute to the pathogenesis or prediction of AF.

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CRediT authorship contribution statement

Oseiwe B. Eromosele: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Ayelet Shapira-Daniels:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Amy Yuan:** Writing – review & editing, Writing – original draft, Visualization, Resources, Methodology, Investigation. **Abdulkareem**

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100439.

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