Life-Course Smoking Trajectories and Risk for Emphysema in Middle Age: The CARDIA Lung Study

To the Editor:

Limited long-term prospective data are available to characterize the effect of low-rate smoking on lung health outcomes, particularly in population-based cohorts. Prior studies have also differed in the measurement of cumulative smoking exposure, with many studies relying on imprecise measurement and long periods of retrospective reporting. Smoking exposure is traditionally indexed by pack-years, and individuals with lifetime smoking thresholds below 10 pack-years are typically excluded from clinical trials for chronic lung disease. However, recent studies have found smoking duration (i.e., years of cigarette smoking) to be superior to cigarettes per day or pack-years in predicting emphysema (1) and mortality (2). Low-rate smoking is increasingly prevalent, with 25% of smokers in the United States currently consuming fewer than 10 cigarettes per day, and a growing body of literature has identified negative health effects associated with low-rate smoking, including cardiovascular disease, cancer, and all-cause mortality (2–4). Using data from the CARDIA (Coronary Artery Risk Development in Young Adults) study, we studied how longitudinal patterns of smoking exposure, based on cigarettes per day reported annually over the course of 25 years of follow-up, are associated with loss of lung function, incident obstructive lung physiology, and computed tomography–measured emphysema.

Methods

CARDIA is a prospective cohort study of the evolution of cardiovascular disease risk factors in 5,115 young adults, initiated in 1985 (5). Participants were invited to complete follow-up exams at Years 2, 5, 7, 10, 15, 20, 25, and 30 with 91%, 86%, 81%, 79%, 74%, 72%, 72%, and 71% retention. Cigarette smoking was evaluated during each in-person CARDIA visit and at annual telephone assessments. We used group-based zero-inflated Poisson trajectory modeling (SAS PROC TRAJ) to identify distinct patterns of smoking among participants by including all ever-smokers who had data recorded on number of cigarettes smoked per day for at least 3 of the 26 annual queries taken from Year 0 to Year 25 (6). Trajectories of cigarettes per day were specified as a function of participant age, using third-order polynomials for both the cigarettes per day Poisson count model and the logit model for predicting extra zeros.

Incident obstructive lung physiology was defined as having a post-bronchodilator FEV_1/FVC ratio $<70\%$ at the Year 30 examination but not at the time of peak lung function. Emphysema at Year 25 was determined by visual review of computed tomography scans (7).

We examined the associations of each lifetime smoking trajectory group with lung function decline and risk for future lung disease, relative to never-smokers. Logistic regression models examined smoking trajectory group as a predictor of emphysema on the Year 25 computed tomography scan and Year 30 obstructive lung physiology, adjusting for age, race–sex group, center, height, body mass index, physician-confirmed asthma, baseline cigarettes per day, and baseline pack-years.

Results

Life-course smoking trajectories are presented in Figure 1. Although the Bayesian Information Criterion indicated a slightly better fit of the seven- versus six-group model, visual inspection of the trajectory group plots suggested greater parsimony in the six-group model presented here. Trajectory group membership was associated with lung function decline in a stepwise manner by smoking exposure, with heavy stable smokers showing the greatest decline in FEV_1 (-42.2 ml/yr; Table 1). Smoking trajectory groups differed in risk for incident obstructive lung physiology, with heavy stable smokers versus never-smokers demonstrating nearly eight times the odds of obstructive disease and more than 20 times the odds of computed tomography emphysema (Table 1). Among the two low-rate smoking groups (low-rate stable smokers and quitters), quitters showed less FEV_1 decline (-33.8 vs. -35.7 ml/yr) and lower emphysema odds than low-rate stable smokers despite having greater mean lifetime pack-years (9.8 vs. 6.4 pack-years, using 20 cigarettes per pack).

Discussion

In a longitudinal, community-based study, we identified a dose–response relationship of smoking exposure with lung function decline and lung disease risk. Trajectory analyses indicated distinct patterns of life-course smoking, which were differentially associated with lung disease risk. Among the two low-rate groups, quitters preserved more lung function and reduced their lung disease risk relative to low-rate stable smokers. These results highlight that there is no safe threshold of sustained smoking with regard to lung disease risk.

The current manuscript extends prior findings on the utility of smoking duration as a predictor of lung health outcomes. Measurement of smoking using pack-years is imprecise (8) and raises concerns of inaccurate reporting and recall bias, especially for individuals whose smoking rate is low or fluctuating. Years smoking may be a more sensitive, reliable, and efficient operational index of smoking exposure in predicting lung disease risk.

Our findings add to a growing body of research on associations between smoking duration and disease risk (2). We identified marked increases in lung disease risk among ever-smokers versus never-smokers, even among low-rate stable smokers, for whom there was

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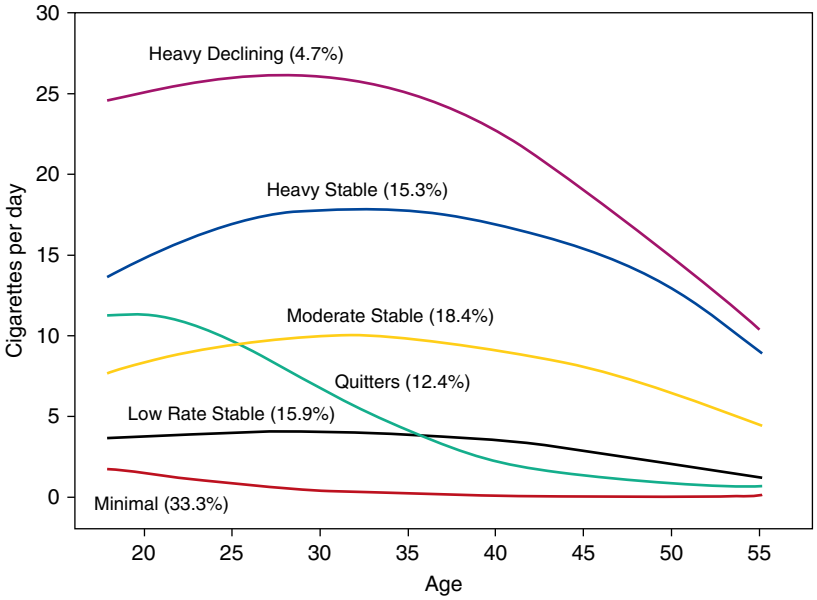

Figure 1. Lifetime smoking trajectories by cigarettes per day reported annually over the course of 25 years. Group-based trajectory modeling was used to generate trajectories of lifetime cigarette smoking. Group compositions were as follows: heavy declining smokers (4.7%; $n = 125$; mean lifetime cumulative pack-years, 38.2), heavy stable smokers (15.3%; $n = 406$; mean lifetime cumulative pack-years, 28.2), moderate stable smokers (18.4%; $n = 488$; mean cumulative pack-years, 15.5), quitters (12.4%; $n = 327$; mean cumulative pack-years, 9.8), low-rate stable smokers (15.9%; $n = 420$; mean cumulative pack-years, 6.4), and minimal smokers (33.3%; $n = 881$; mean cumulative pack years, 2.1).

nearly three times the risk for incident obstruction and more than an eightfold increase in computed tomography emphysema risk. As missing data were more common among participants with greater smoking exposure, our analyses are biased toward the null, and effect sizes likely underestimate the true disease risk among heavy smokers. Further, although our approach adjusted for participant-level peak lung function, we were unable to examine the main effect of peak lung function on subsequent disease risk (9, 10).

Given that an increasing proportion of individuals smoke at a low or intermittent rate (3), our findings have important public health implications. As compared with never-smokers, low-rate smokers demonstrated increased disease risk, despite a relatively low threshold of lifetime smoking exposure (6.4 pack-years). Targeted messaging is needed to reiterate the lung health risk of sustained smoking at any level. In addition, healthcare providers should underscore the lung health benefit of smoking cessation over and above smoking reduction (i.e., cutting down on cigarettes per day without intention to quit). Although smoking reduction may be a positive initial step toward cessation, prospective studies demonstrate limited lung health benefits of smoking reduction alone (11). This is likely a result of changes in smoking topography, in which smokers inhale more deeply and/or smoke more puffs of each cigarette to compensate for a lower number of cigarettes per day. Our findings are consistent with the message that quitting, and not cutting down, is the most effective method of reducing lung disease risk.

Smoking influenced lung disease risk in a dose-dependent manner. There was no safe threshold for smoking intensity on lung disease risk, and even low-rate smokers were at increased risk for future lung disease. These results underscore the benefit of complete abstinence from smoking, even among low-rate smokers, on respiratory outcomes. ■

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Amanda R. Mathew, Ph.D.
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Surya P. Bhatt, M.D.
University of Alabama–Birmingham
Birmingham, Alabama

Laura A. Colangelo, M.S.
Norrina B. Allen, Ph.D.
Northwestern University Feinberg School of Medicine
Chicago, Illinois

David R. Jacobs, Jr., Ph.D.
University of Minnesota School of Public Health
Minneapolis, Minnesota

Reto Auer, M.D.
University of Bern
Bern, Switzerland
and
University of Lausanne
Lausanne, Switzerland

Mark T. Dransfield, M.D.
University of Alabama–Birmingham
Birmingham, Alabama

Brian Hitsman, Ph.D.
Northwestern University Feinberg School of Medicine
Chicago, Illinois

George R. Washko, M.D.
Brigham and Women's Hospital
Boston, Massachusetts

Table 1. Smoking Trajectory Group, Mean FEV_1 Decline, and Association (Covariate Adjusted Odds Ratio) with Incident Lung Disease

Smoking Trajectory Group	FEV_1 Decline (*ml/yr*) (SEM)	Incident Lung Disease				
		Prebronchodilator Obstructive [*OR (95% CI)*]	Post-bronchodilator Obstructive [*OR (95% CI)*]	Centrilobular Emphysema [*OR (95% CI)*]	Paraseptal Emphysema [*OR (95% CI)*]	Any Emphysema (Paraseptal or Centrilobular) [*OR (95% CI)*]
Never smokers	−32.48 (0.35)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Minimal smokers	−32.34 (0.53)	1.36 (0.98–1.88)	1.42 (0.86–2.35)	1.81 (0.64–5.15)	1.59 (0.62–4.09)	1.44 (0.66–3.13)
Low-rate stable smokers	−35.70 (0.83)	2.44 (1.59–3.72)	2.80 (1.55–5.06)	9.60 (4.04–22.84)	11.24 (5.42–23.31)	8.45 (4.52–15.82)
Quitters	−33.80 (0.93)	1.19 (0.69–2.03)	2.03 (1.02–4.06)	5.85 (2.13–16.04)	3.79 (1.46–9.87)	3.44 (1.53–7.71)
Moderate stable smokers	−38.46 (0.87)	3.15 (2.06–4.81)	5.34 (3.10–9.19)	25.72 (11.63–56.88)	21.27 (10.59–42.73)	20.10 (11.15–36.22)
Heavy stable smokers	−42.19 (1.12)	4.20 (2.52–6.98)	7.44 (3.94–14.06)	37.56 (15.87–88.89)	25.37 (11.68–55.18)	26.01 (13.36–50.63)
Heavy declining smokers	−41.29 (1.97)	3.04 (1.36–6.76)	7.54 (2.92–19.47)	35.53 (11.33–111.38)	26.98 (9.25–78.70)	25.40 (9.82–65.67)

Definition of abbreviations: CI = confidence interval; OR = odds ratio; ref = reference.

FEV_1 decline values reflect mean (SEM) adjusted annualized decline in lung function from peak measurement to Year 30. Never-smokers were the reference group for all models. Obstructive lung disease indicates FEV_1/FVC value <70% at the Year 30 examination but not at the time of peak lung function. Covariates are baseline age, race–sex group, center, height, baseline body mass index, physician-confirmed asthma, baseline cigarettes per day, and baseline pack-years.

Ravi Kalhan, M.D.*
Northwestern University Feinberg School of Medicine
Chicago, Illinois

ORCID ID: 0000-0003-2443-0876 (R.K.).

*Corresponding author (e-mail: r-kalhan@northwestern.edu).

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IL-5 Levels in Nasosorption and Sputosorption Correlate with Sputum Eosinophilia in Allergic Asthma

To the Editor:

Monoclonal antibodies that block type 2 cytokines (e.g., IL-4, IL-5, and IL-13) are promising new therapies for asthma (1). However, these agents need to be targeted to selected patients with asthma, where biomarker assessment of airway samples may support stratification of patients into molecular endotypes (2). Thus, we measured cytokine and chemokine mediator levels in nasosorption samples and by using a novel method of sputosorption from induced sputum. Nasal and sputum mediators were then compared with sputum eosinophil levels. A group of 29 allergic asthmatics (AAs) not receiving oral, inhaled, or intranasal corticosteroids or leukotriene modifiers in the last 3 months (with positive skin prick tests, mean baseline FEV_1 of 79.3 ± 18.0, and FEV_1 reversibility), one of whom did not report a history of allergic rhinitis, were recruited. Dust mite extracts were the most commonly sensitized antigens: *Dermatophagoides pteronyssinus* (93.1%), *Dermatophagoides farinae* (79.3%), and *Blomia tropicalis* (75.8%). These were compared with a control group of 17 nonatopic healthy control patients (HC) with no history of allergic rhinitis and a mean baseline FEV_1 of 94.1 ± 11.4. Participants were nonsmokers and were free of upper or lower respiratory infections for the last 4 weeks. Subjects were excluded if they could not safely provide specimens; by the presence of other medical conditions; because of use of concomitant medication, tobacco, or illicit drugs; and if women were pregnant or breastfeeding. The study was approved by the Ethical Committee of Universidade Federal de Santa Catarina (Brazil) on March 10, 2008.

Methods

Nasosorption was performed by placing two strips of synthetic absorptive matrix (Leukosorb, Pall Life Sciences), measuring 7 × 30 mm each, against the inferior turbinate for 2 minutes (Conformité Européene–marked nasosorption sampling devices are now available sterile and allergen-free from Mucosal Diagnostics Ltd.) (3, 4). Sputum was induced by inhalation of hypertonic saline, after which the sample was poured onto a Petri dish, and the viscid portions apparently free of salivary contamination were macroscopically selected. One portion of the selected material was used for cytospin preparation and differential cell count. The remaining portion was used for sputosorption, whereby two synthetic absorptive matrix strips, 7 × 30 mm each, overlaid the sputum for 2 minutes.

Once removed, the synthetic absorptive matrixes were immersed in 200 μl assay buffer (Millipore) + 4 μl DPP Protease Inhibitor-IV (Millipore), placed in the filter cup within a microcentrifuge tube, and centrifuged (10 min, 16,000 × *g*, 4°C); the supernatant aliquots were stored at −80°C. Mediators were quantified using a Luminex 200 IS Analyzer (Luminex Corp.), and results were expressed in picograms per milliliter. Continuous data were evaluated by the Shapiro-Wilk normality test and presented as median and interquartile ranges and tested for significance by Mann-Whitney *U* tests. Correlations were performed by Spearman rank correlation tests with Benjamini-Hochberg *post hoc* correction.

Sputum eosinophil percentage levels from AAs were significantly higher than those of HCs (Figure 1A, left; $P < 0.001$). A panel of cytokines and chemokines were measured in nasosorption and sputosorption samples, and the corresponding levels are shown for individual patients (Figure 1B), noting that sputum and nasal IL-5 levels were significantly higher in AAs relative to HCs (Figure 1A, right; $P < 0.001$), whereas AAs exhibited significantly lower

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