



Nasal Mucociliary Clearance in Smokers: A Systematic Review

Awal Prasetyo^{1,2} Udadi Sadhana² Jethro Budiman^{1,2,3}

¹Department of Biomedical Science, Faculty of Medicine, Diponegoro University, Semarang, Indonesia

²Department of Anatomic Pathology, Faculty of Medicine, Diponegoro University - Dr. Kariadi Hospital, Semarang, Indonesia

³Department of Emergency Unit, Panti Wilasa Citarum Hospital, Semarang, Indonesia

Address for correspondence Jethro Budiman, MD, Faculty of Medicine, Diponegoro University, Jl. Prof. Sudharto, SH Tembalang, Semarang 50275, Indonesia (e-mail: jethrobudiman93@gmail.com).

Int Arch Otorhinolaryngol 2021;25(1):e160–e169.

Abstract

Introduction Smoking is one of the most important causes of mortality and morbidity in the world, as it is related to the risk factor and etiology of respiratory-tract diseases. Long-term smoking causes both structural and functional damage in the respiratory airways, leading to changes in nasal mucociliary clearance (NMC).

Objectives The aim of the present study was to look systematically into the current literature and carefully collect and analyze results to explore NMC in smokers.

Data Synthesis Two independent reviewers conducted a literature search on some Electronic database: Pubmed, Medline, Ebsco, Springer Link, Science Direct, Scopus, and Proquest searching for articles fulfilling the inclusion and exclusion criteria. The lead author independently assessed the risk of bias of each of the included studies and discussed their assessments with the other two authors to achieve consensus. Of the 1,654 articles identified in the database search, 16 met the criteria for this review. Most of the articles (15 out of 16) showed the impairment of NMC in smokers.

Conclusion The present systematic review suggests that there is an impairment of NMC in smokers. The impairment is not only observed in cigarette smoking, but also in passive smoking, bidi smoking, electronic smoking, and hookah smoking. The impairment of NMC in chronic exposure to smoking is caused by the ciliotoxic effect, hypersecretion and viscoelastic change of mucous, airway surface liquid depletion, increased oxidative stress, and deteriorations in the inflammatory and immune systems.

Keywords

- ▶ nasal mucociliary clearance
- ▶ smokers
- ▶ smoking

Introduction

Smoking is one of the most important causes of mortality and morbidity in the world, especially in developing countries.^{1–4} According to the World Health Organization (WHO), there are around 1.1 billion smokers in the world, and half of

them die every year (2015).¹ There are many types of smoking, such as cigarette smoking, bidi smoking, hookah smoking, electronic cigarette (EC) smoking, passive smoking, and many more.^{2–7} All of these types of smoking are related to the risk factor and etiology of many health problems, especially in the respiratory tract. In the respiratory tract,

received
October 15, 2019
accepted
December 18, 2019
published online
April 24, 2020

DOI <https://doi.org/10.1055/s-0040-1702965>.
ISSN 1809-9777.

© 2020. Fundação Otorrinolaringologia. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)
Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

smoking is related to upper respiratory tract infection, asthma, chronic obstructive pulmonary disease, nasopharyngeal cancer, and lung cancer.^{2,8-10} Smoking is a significant risk factor for respiratory diseases, considering its ability to lead to an alteration of nasal mucociliary clearance (NMC).^{2,11,12}

Nasal mucociliary clearance is the primary innate defense mechanism of the nose and paranasal sinuses, and it consists of mucous layer, airway surface liquid layer, and ciliary epithelia.^{2,13-15} Mucus produced by the goblet cells of the mucosa is required for binding of the airborne pathogens (such as inhaled microbes and irritants). Ciliated epithelial cells are expectorated or swallowed. Normal functioning of the NMC requires high frequency, coordinated, and directional ciliary beating (metachronal waves) as well as proper mucus secretion and airway surface liquid. Ciliary beat frequency (CBF) was shown to be the major determinant of NMC efficiency.^{2,13-15} Nasal mucociliary clearance is influenced by physiological factors, such as mucus production and CBF; anatomic factors, such as nasal airflow and patency of the sinus ostia in the prechambers; and biochemical factors, such as mucus composition.^{2,13-16}

Various factors, like aging, body temperature, drugs (like adrenaline, acetylcholine, corticosteroid, and intranasal drug), tobacco use and smoking, and environment factors (like pollutant, smoke, and dust) affect this system, besides pathological conditions such as rhinitis allergy, acute or chronic rhinosinusitis, and deviated nasal septum.^{2,17-19} Any dysfunction in this defense system increases the inflammatory process and stasis of airborne pathogens, and the respiratory system becomes prone to obstructive airway diseases and infections.^{2,11,12} Long-term smoking causes both structural and functional damage in the respiratory airways, leading to changes in NMC.^{2,4,11,12,20}

The adverse effects of smoking on NMC have been reported and explained in various studies, but we could not find any systematic review about NMC in smokers. The aim of the present study was to look systematically into the current literature and carefully collect and analyze results to explore NMC in smokers.

Review of the Literature

Scope of the Review: Inclusion and Exclusion Criteria

Inclusion criteria:

1. Publication type:
 - full-text articles discussing NMC in smokers
 - primary studies of every design (case study, case series, cross sectional, case control, cohort, clinical trial)
2. Language of publication: English
3. Time of publication: January 2000 to August 2019
4. Methodology: studies included must explain NMC in smokers
5. Population: human at any age

Exclusion criteria:

1. Population: in-vitro samples
2. Objective and outcome measures are not relevant (are not about NMC in smokers)
3. Confounding variables are related to outcome of NMC in smokers

Literature Search

The current systematic review was conducted in accordance with Cochrane handbook for systematic reviews and is reported by using the guidelines of the preferred reporting items for systematic review and meta-analysis (PRISMA).^{21,22} A systematic search strategy was conducted in the following electronic databases: Pubmed, Medline, Ebsco, Springer Link, Science Direct, Scopus, and Proquest. The search was conducted using the following keywords for title and abstract: *nasal mucociliary clearance* OR *nasal mucociliary transport* AND *smoke* OR *smoker* OR *smoking* OR *cigarette*. In the Pubmed database, the keywords were searched through the [tiab] and [MeSH] tags. No limitation was applied during the search. The reference lists of the retrieved papers were also examined to avoid missing any published data.

Data Collection and Analysis

Studies were selected for retrieval after two independent reviewers (A. P. and U. S.) had collected titles and abstracts identified in the electronic search. The results of the two reviewers were compared by a third independent reviewer (J. B.), and any differences of opinion were resolved by discussion. Full papers from potential studies were independently assessed by the investigators (A. P. and U. S.).

All studies selected for this systematic review were screened by two reviewers independently to validate the results (A. P. and U. S.). The data from all retrieved studies are

Table 1 Newcastle-Ottawa scale (prospective study)

No.	First author, year	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
1.	Dülger et al, 2018 ⁴			*	*		*	*	*	5
2.	Utiyama et al, 2016 ¹¹	*	*	*	*		*	*	*	7
3	Yadav et al, 2014 ⁷			*	*	**	*	*	*	7
4	Ramos et al, 2011 ³¹			*	*	**	*	*	*	7

*Maximum points for comparability were 2.

presented in the summary table (►Table 1) featuring key points of each study. The following data were collected: first author and year, study design, sample, sample characteristic (age and gender), smoking characteristic (type, years of smoking, cigarettes-/day or packs/year), NMC measurement test, and result.

Quality Assessment

The lead author independently assessed the risk of bias of each of the included studies and discussed their assessments with other two authors to achieve consensus. The Newcastle-Ottawa scale adapted for cross-sectional studies, Newcastle-Ottawa scale cohort version, and the Cochrane risk of bias were used to assess the methodological quality of the studies.^{21,23-25} The Newcastle-Ottawa scale adapted for cross-sectional studies was used to assess cross sectional studies; interpretation of the total score was: 9 to 10 points were considered very good studies, 7 to 8 points were considered good studies, 5 to 6 points were considered satisfactory studies, and 0 to 4 were considered unsatisfactory studies.²³ The Newcastle-Ottawa scale cohort version was used to assess prospective studies; interpretation of the total score was: ≥ 7 points were considered good studies, 5 to 6 points were considered fair studies, and < 5 points were considered poor studies.²⁴⁻²⁷ The Cochrane risk of bias was used to assess randomized control trial studies, whose results were either high risk or some concerns or low risk.²¹

Results

Selection of Articles for Review

►Fig. 1 summarized the identified, screened, and included articles for review. Initially, 1,622 peer-reviewed articles were identified from electronic databases, and an additional

32 articles were identified through other sources (search engine). After removing duplicates, 384 articles remained for title and abstract screening. Articles that did not meet the inclusion and exclusion criteria were not further screened. Twenty-six articles were screened for eligibility, 16 of which met all the inclusion criteria.

Assesment of Study Validity (Risk of Bias)

All eligible studies were associated with NMC in smokers. ►Table 2 provides quality scores for cross-sectional studies; all studies that got 6 to 8 points were included in the satisfactory and good studies category. ►Table 1 provides quality scores for prospective studies; all studies that got 5 to 7 points were included in the fair and good studies category. ►Table 3 provides quality scores for randomized control trial studies; all studies presented results of some concerns or low risk.

Study Characteristic

Study characteristics for the included studies could be seen in ►Table 4. The majority of the studies followed the cross-sectional design (11 out of 16). Most of the samples were in productive age and reported cigarette smoking. Nasal mucociliary clearance measurement tests mostly used saccharin transfer/transit time test.

Most of the studies showed the impairment of NMC in smokers. Nasal mucociliary clearance in cigarette smokers was explained in 13 studies (11 studies reported significant impairment in smokers, 1 study reported insignificant impairment in smokers, 1 studies reported that the NMC value in smokers was significantly lower than in non-smokers). Nasal mucociliary clearance in passive smokers was explained in three studies, and all of the studies reported that the NMC value in passive smokers was significantly

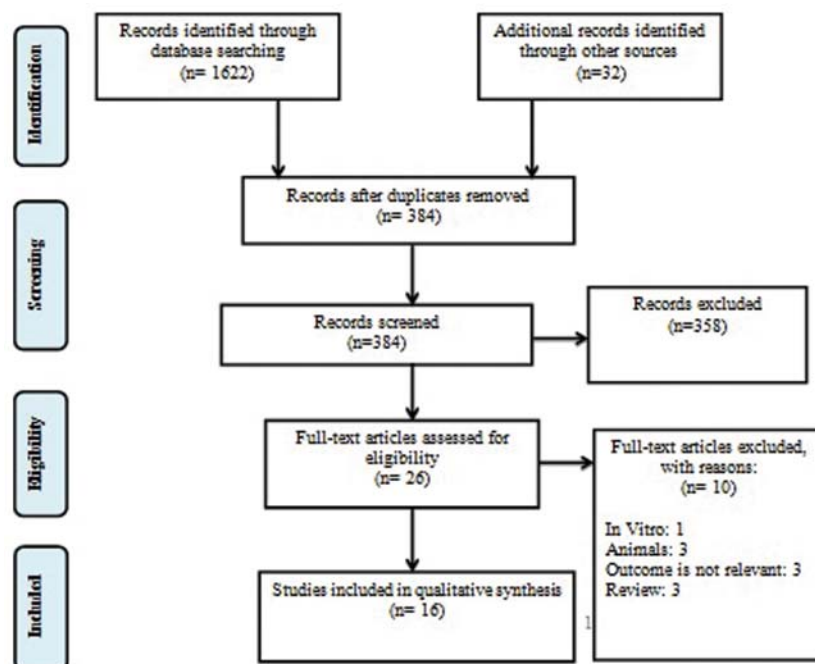


Fig. 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA).²²

Table 2 Newcastle-Ottawa scale adapted for cross-sectional studies

No.	First author, year	Selection				Comparability	Outcome		Total
		1	2	3	4		1	2	
1.	Arıçgil M and Arbağ, 2018 ⁵			*	**		**	*	6
2.	Paul et al, 2018 ³		*	*	**		**	*	7
3.	Solak et al, 2018 ²			*	**		**	*	6
4.	Uzeloto et al, 2018 ⁴⁸			*	**		**	*	6
5.	Habesoglu et al, 2015 ²⁹			*	**		**	*	6
6.	Pagliuca et al, 2015 ¹²			*	**		**	*	6
7.	Baby et al, 2014 ¹⁷			*	**		**	*	6
8.	Nicola et al, 2014 ²⁸			*	**		**	*	6
9.	Xavier et al, 2013 ²⁰			*	*	*	**	*	7
10.	Habesoglu et al, 2012 ³⁸			*	**	**	**	*	8
11.	Proença et al, 2011 ³⁵			*	**	**	**	*	8

*Maximum points for selection number 4, comparability, and outcome number 1 were 2.

Table 3 Cochrane risk of bias: Kumral TL, 2016⁶

No.	Domain	Description of domain	Results
1.	Domain 1	risk of bias arising from the randomization process	some concerns
2.	Domain 2	risk of bias due to deviations from the intended interventions (<i>effect of adhering to intervention</i>)	some concerns
3.	Domain 3	missing outcome data	low risk
4.	Domain 4	risk of bias in measurement of the outcome	low risk
5.	Domain 5	risk of bias in selection of the reported result	low risk

higher than in non-smokers. Nasal mucociliary clearance in bidi, hookah, and electronic smoking, respectively, was explained in only one study.

Discussion

Nasal Mucociliary Clearance in Smokers

Most of the studies (15 out of 16 studies) showed the impairment of NMC in smokers. One study (Nicola et al, 2014)²⁸ reported that the NMC value in smokers was lower than non-smokers. Nicola et al (2014) speculated that young smokers may have a protective response to cigarette smoking (increase of the CBF and transport system).²⁸ The impairment was not only observed in active cigarette smoking, but also in bidi, EC, hookah, and passive smoking. This happens because all of them contain harmful constituents that affect NMC. The saccharin transfer time test was used in many studies to evaluate NMC because it is easy, safe, and inexpensive.^{4,5,29}

Various chemicals present in cigarette smoke, including acrolein, formaldehyde, carbon monoxide, nicotine, cotinine, acetaldehyde, phenol, and potassium cyanide, have been identified as having high toxicity to NMC.^{7,30} The gaseous phase of cigarette smoke contains high concentrations of free radicals (>10¹⁵ molecules per puff), resulting in increased oxidative stress that, in turn, causes changes in the structure and function of the NMC.^{31,32} The impairment of NMC in chronic exposure to cigarette smoke is caused by the ciliotoxic effect, hypersecretion and viscoelastic change of mucous (particularly of more viscous properties), airway surface liquid depletion, increased oxidative stress, and deteriorations in the inflammatory and immune systems (increased of macrophages, neutrophil, and proinflammatory cytokines), which cause elongation of the NMC time and stagnation of toxic substances.^{4,11,17,20} The ciliotoxic effect of cigarette smoking reduces cilia genesis, paralyzes ciliary beating activity (reduces CBF), is related to abnormality in the cilia ultrastructure, and decreases the number of cilia.^{4,11} Cigarette smoking also causes metaplastic changes of the respiratory mucosa, with increase in the number and size of the goblet cells that leads to increased production of respiratory airway secretions.^{12,20} The acrolein in cigarette smoke reduces the cystic fibrosis transmembrane conductance regulator (CFTR) gene expression, resulting in airway surface liquid depletion and mucus stasis in the airway epithelium.^{20,33,34} Other studies also showed that chronic exposure to cigarette smoke stimulates the parasympathetic nervous system (glandular hypersecretion and vasodilatation), inhibits secretion of Cl⁻ and K⁺ conductance in normal respiratory epithelium cells, alters epithelial salts and water transport, alters morphology of the epithelium in the entire of respiratory tract (metaplasia with keratinisation), reduces cells viability, and induces cell apoptosis (opposite mitogenic effect or proapoptosis depending on the concentration of smoke and impairment of cell regeneration in respiratory epithelium), induces matrix metalloproteinases (zinc

Table 4 Study characteristics

No.	First author, year	Study design	Sample (N)	Sample characteristic: age (year), gender (male, female)	Smoking characteristic: type, years of smoking, cigarettes/day and/or packs/year	NMC measurement test	Result
1.	Arıcıll and Arbağ , 2018 ⁵	Cross-sectional	Non-smokers: 40 Smokers I (once every week): 20 Smokers II (more than once a week/2-5 session-week): 18	Age: 18-41 years Non-smokers: 27.5 ± 6.4 Smokers I: 26.9 ± 6.8 Smokers II: 27.7 ± 6.3 Gender Non-smokers: 22,18 Smokers I: 11,9 Smokers II: 10,8	Hookah smoking	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was significantly higher than in non smokers ($p < 0.001$). NMC value (STT) in the smokers-II group was significantly higher than in the smokers-I group and non-smokers (19.2 ± 2.5; 11.9 ± 2.8; 11.1 ± 3; $p < 0.001$).
2.	Dulger et al, 2018 ⁴	Prospective study (2 years period)	Non-smokers: 35 Smokers: 50	Age: 18-65 years Non-smokers: 35.8 Smokers: 31.4 Gender Non-smokers: 23,12 Smokers: 30,20	Cigarette smoking Cigarettes/day: 20.6 Packs/year: ≤10 packs/year: 11 10-20 packs/year: 28 20-30 packs/year: 5 ≥ 30 packs/year: 6	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was significantly higher than in non-smokers (12 minutes, 9 minutes; $p < 0.001$). No statistically significant difference in nasal MCC value and packs/year ($p = 0.943$).
3.	Paul et al, 2018 ³	Cross-sectional	Non-smokers: 20 Cigarette smokers: 20 Bidi smokers: 20	Age: 20-40 years Non-smokers: 29.3 ± 6.25 Cigarette smokers: 31.2 ± 5.42 Bidi smokers: 30.2 ± 6.77 Gender: male	Cigarette and Bidi smoking Packs/year: Cigarette smokers: 4.63 ± 2.74 Bidi smokers: 7.5 ± 5.1	Methylene blue dye test	<ul style="list-style-type: none"> NMC value was significantly decreased in bidi smokers as compared with cigarette smokers and non-smokers (59.25 ± 12.38 mm; 67 ± 5.48 mm; 67.89 ± 4.10 mm; $p < 0.05$). Multivariate analysis revealed a significant association between NMC and bidi smoking, number of cigarettes or bidis smoked per day, and packs/year ($p < 0.05$).
4.	Solak et al, 2018 ²	Cross-sectional	Non-smokers: 74 Smokers: 123	Age: 18-55 years Non-smokers: 38.79 ± 9.66 Smokers: 40.33 ± 8.94 Gender Non-smokers: 58,16 Smokers: 23,100	Cigarette smoking Years of smoking: 24.31 ± 9.66 Cigarettes/day: 18.45 ± 8.78 Packs/year: 28.49 ± 15.68	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was significantly higher than in non-smokers (536.19 ± 254.81 seconds 320.43 ± 184.98 seconds $p < 0.001$). Positive correlation between STT and number of cigarettes/day ($p: 0.012$, $r: 0.225$), STT and packs/year ($p: 0.001$, $r: 0.296$), STT and years of smoking ($p = 0.027$, $r = 0.200$).
5.	Uzeloto et al, 2018 ⁴⁸	Cross-sectional	Non-smokers: 69 Smokers: 70	Age: 30-50 years Non-smokers: 39.5* Smokers: 41* Gender Non-smokers: 32,37 Smokers: 33,37 *: median	Cigarette smoking Years of smoking: 21.50* Cigarettes/day: 20.00* Packs/year: 22.00* *: median	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was insignificantly higher than in non-smokers (9.7 minutes; 9.145 minutes; $p > 0.05$).
6.	Kumral et al, 2016 ⁶	Prospective randomized	Non-smokers: 40 Smokers: 58	Age Non-smokers: 38.0 ± 8.2	EC smoking duration: 3 months	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in electronic cigarette was significantly higher than in

Table 4 (Continued)

No.	First author, year	Study design	Sample (N)	Sample characteristic: age (year), gender (male, female)	Smoking characteristic: type, years of smoking, cigarettes/day and/or packs/year	NMC measurement test	Result
7.	Utiyama et al, 2016 ¹¹	single-blind clinical trial	Quitters: 20 Smokers: 13	Smokers: 33.9 ± 7.9 Gender Non-smokers: 16,14 Smokers: 18,24 Age Quitters: 51 ± 9 Smokers: 52 ± 10 Gender Quitters: 9,11 Smokers: 6,7	Cigarette smoking Packs/year: Quitters: 40 ± 27 Smokers: 45 ± 28	Saccharin transfer/transit time test	non-smokers (11.93 ± 1.81; 10.36 ± 1.61; p = 0.0003). • NMC value (STT) in smokers showed increases of impairment after 12 months observation (±14 minutes; ±15 minutes). • NMC value (STT) in quitter showed decreases of impairment after 12 months observation (±15 minutes, ± 10 minutes).
8.	Habesoglu et al, 2015 ²⁹	Cross-sectional	Group I (control): 18 Group II (living with at least one adult smoker outside the house): 15 Group III (living with at least one adult smoker inside the house): 17	Age 6–14 years Group I: 10.22 ± 2.39 Group II: 11.2 ± 1.97 Group III: 10.65 ± 2.09 Gender Group I: 9,9 Group II: 7,8 Group III: 9,8	Passive smoking	Saccharin transfer/transit time test	• NMC value (STT) in group II was insignificantly higher than in group I (p = 0.067). • NMC value (STT) in group III was significantly higher than in group I (p < 0.001). • NMC value (STT) in group III was insignificantly higher than in group II (p = 0.173). • NMC value (STT) in groups I, II, and III: 7.33 ± 2.91 minutes, 10.00 ± 4.78 minutes, 12.41 ± 3.44 minutes.
9.	Pagliuca et al, 2015 ¹²	Cross-sectional	Non-smokers: 30 Ex-smokers: 30 Smokers: 30	Age Non-smokers: 53.17 ± 5.53 Ex-smokers: 50.73 ± 6.51 Smokers: 51.97 ± 6.02 Gender Non-smokers: 19,11 Ex-smokers: 23,7 Smokers: 24,6	Cigarette smoking Cigarettes/day: ex-smokers: 25 ± 7.76 smokers: 24,67 ± 6.3	Saccharin transfer/transit time test	NMC value (STT) in smokers was significantly higher than in others (smokers: 15.6 minutes, ex-smokers: 11.77 minutes, non-smokers: 11.71 minutes, p < 0.0001).
10.	Baby et al, 2014 ¹⁷	Cross-sectional	Non-smokers: 30 Smokers: 30	Age: 21–40 years Non-smokers: 26.8 ± 1.2 Smokers: 24.96 ± 1 Gender: male	Cigarette smoking	Saccharin transfer/transit time test	• NMC value (STT) in smokers was significantly higher than in the non-smokers group (481.2 ± 29.83 seconds 300.32 ± 17.42 seconds; p < 0.01). • A statistically significant increase in the NMC value was observed with an increase in duration of smoking habit (NMC in smoking < 1 year: 492.25 ± 79.93 seconds; 1–5 years: 516.7 ± 34.01 seconds > 5 years: 637.5 ± 28.49 seconds p = 0.0000).

(Continued)

Table 4 (Continued)

No.	First author, year	Study design	Sample (N)	Sample characteristic: age (year), gender (male, female)	Smoking characteristic: type, years of smoking, cigarettes/day and/or packs/year	NMC measurement test	Result
11.	Nicola et al, 2014 ²⁸	Cross-sectional	Non-smokers: 32 Smokers < 2.5 packs/year: 20 Smokers > 2.5 packs/year: 20	Age: 18-35 years Non-smokers: 21 Smokers < 2.5 packs/year: 19 Smokers > 2.5 packs/year: 24 Gender: Non-smokers: 29, 3 Smokers < 2.5 packs/year: 20, 0 Smokers > 2.5 packs/year: 17, 3	Cigarette smoking Years of smoking Smokers < 2.5 packs/year: 3* Smokers > 2.5 packs/year: 7* Packs/year: Smokers < 2.5 packs/year: 0.7* Smokers > 2.5 packs/year: 6* *; median	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was significantly lower than in non-smokers (5.9 ± 3.1 minutes; 7.7 ± 4.1 minutes; p = 0.033).
12.	Yadav et al, 2014 ⁷	Prospective study (five years duration)	Non-smokers: 50 Active smokers: 50 Passive smokers: 50	Age: 20-50 years Non-smokers: 38,7 Active smokers: 39,1 Passive smokers: 35,1 Gender: Non-smokers: 44,6 Active smokers: 42,8 Passive smokers: 24,26	Cigarette smoking (active and passive)	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers (active and passive) was significantly higher than in non-smokers (23.08 ± 4.60; 20.31 ± 2.51; 8.57 ± 2.12; p < 0.0003). NMC value (STT) in active smokers was insignificantly higher than in passive smokers (p = 0.03).
13.	Xavier et al, 2013 ²⁰	Cross-sectional	Non-smokers: 24 Light smokers: 14 Moderate smokers: 34 Heavy smokers: 27	Age: Non-smokers: 50 ± 11 Light smokers: 51 ± 15 Moderate smokers: 49 ± 7 Heavy smokers: 46 ± 8 Gender: Non-smokers: 7,17 Light smokers: 5,9 Moderate smokers: 14, 20 Heavy smokers: 13, 14	Cigarette smoking Years of smoking Light smokers: 32 ± 17 Moderate smokers: 29 ± 9 Heavy smokers: 32 ± 8 Cigarettes/day: Light smokers: 9 ± 1 Moderate smokers: 18 ± 3 Heavy smokers: 39 ± 11 Packs/year index: Light smokers: 17 ± 10 Moderate smokers: 27 ± 11 Heavy smokers: 59 ± 44	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in moderate and heavy smokers was significantly higher (p = 0.0001) than in light smokers and non-smokers. A positive correlation was observed between STT and cigarettes/day (r = 0.3; p = 0.02).
14.	Habesoglu et al, 2012 ³⁸	Cross-sectional	Non-smokers: 15 Passive smokers: 15 Active smokers: 17	Age: 17-47 years Active smokers: 28.12 ± 10.79 Passive smokers: 29.17 ± 12.18 Non-smokers: 27.92 ± 11.29 Gender: Active smokers: 11,6 Passive smokers: 8,7 Non-smokers: 6,9	Cigarette smoking (active and passive)	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in active smokers was significantly higher than in passive smokers and non-smokers (23.59 ± 12.41 minutes; 12.6 ± 4.67 minutes; 6.4 ± 1.55 minutes; p < 0.01). NMC value (STT) in the passive group was significantly higher than in the non-smokers group (p < 0.01).
15.	Proenca et al, 2011 ³⁵	Cross-sectional	Non-smokers: 19 Smokers: 19	Age: Non-smokers: 47 ± 11 Smokers: 51 ± 16 Gender:	Cigarette smoking Years of smoking: 33 ± 11 Cigarettes/day: 27 ± 11 Packs/year index: 44 ± 25	Saccharin transfer/transit time test	<ul style="list-style-type: none"> NMC value (STT) in smokers was significantly higher than in non-smokers 8 hours after smoking (16 ± 6 minutes; 10 ± 4 minutes, p = 0.005) and insignificantly higher immediately after

Table 4 (Continued)

No.	First author, year	Study design	Sample (N)	Sample characteristic: age (year), gender (male, female)	Smoking characteristic: type, years of smoking, cigarettes/day and/or packs/year	NMC measurement test	Result
16.	Ramos et al, 2011 ³¹	Prospective study (1 year-period)	Non-smokers: 33 Smokers: 33	Age Non-smokers: 52 ± 14 Smokers: 49 ± 12 Gender: Non-smokers: 18, 15 Smokers: 12,21	Cigarette smoking Years of smoking: 21 ± 8 Cigarettes/day: 20 ± 10 Packs/year index: 44 ± 25	Saccharin transfer/transit-time test	<p>smoking (11 ± 6 minutes; 10 ± 4 minutes; <i>p</i> = 0.87).</p> <ul style="list-style-type: none"> NMC value (STT) 8 hours after smoking was correlated positively with age (<i>r</i> = 0.59; <i>p</i> = 0.007), cigarettes per day (<i>r</i> = 0.53; <i>p</i> = 0.02) and packs/year index (<i>r</i> = 0.74; <i>p</i> = 0.0003). NMC value (STT) in smokers was significantly higher than in non-smokers (±14 minute, ±8 minutes, <i>p</i> = 0.002). NMC value (STT) decreased to within normal range on day 15 after smoking cessation (±10 minutes, <i>p</i> < 0.01), and remained in the normal range until the end of study period (±8 minutes).

Abbreviations: min, minutes; mm, millimeters; NMC, nasal mucociliary clearance; s, seconds; STT, saccharin transfer time.

dependent endopeptidase) that relates to the loss of NMC function and the epithelial disruption exposed to smoke via direct cell-to-cell or cell-to-basement membrane connections, and increases protein kinase-C (PKC) activity related to inhibitory effect on CBF.^{7,30,35-37}

Pronça M (2011) reported that the NMC value in smokers was insignificantly higher immediately after smoking and significantly higher than in non-smokers 8 hours after smoking. The difference between them may be an effect of nicotine on the sympathetic nervous system, which accelerates CBF. However, the circulating nicotine is metabolized in 2 hours, indicating that, after this period, the stimulatory effect ceases, and the smoker's CBF (or the efficiency of transport and defense mechanism) returns to its "normal" (impaired) state.³⁵

The improvement of NMC due to smoking cessation is caused by normalization of the cilia structure, genesis, and also ciliary beating function; changes of the cytomorphological features, such as fewer columnar cells, less mucus and reduced epithelial-cell metaplasia; restoration of the ionic transport function and mucus hydration at the basolateral membrane (increased mucus clearability); and detoxification of hydrogen peroxide through the activity of the glutathione peroxidase (antioxidant enzyme).^{11,31}

The finding of increased NMC value in passive smokers indicates that passive smokers present impairment of the NMC just like active smokers.^{7,29,38} It has been observed that chronic passive exposure to cigarette smoke in the household has slightly higher serum cotinine, which is a metabolite of nicotine that decreases ciliary activity.⁷ Other studies also reported that passive smoking has a negative impact on cilia regeneration, as it impairs the structure of the nasal mucosa (patchy loss of cilia, generalized loss of cilia, squamous metaplasia, vascular congestion, hyperplasia of goblet cells and seromucinous acini), and impairs epithelial ion transport (inhibit chloride secretion and basolateral K⁺ conductance), which can negatively affect NMC.^{7,29,38}

Bidi is a hand-rolled tobacco product, and, unlike cigarettes, it is devoid of a filter (the filter of a cigarette functions as a barrier, by preventing the noxious smokes from reaching the nasal cavity).^{3,39} Although a bidi contains a lower amount of tobacco compared with a cigarette, it produces higher levels of noxious substances like nicotine, carbon monoxide, tar, phenols, and ammonia and results in a higher degree of impairment and addiction.^{3,40} It has been reported that bidi produces three times the amount of carbon monoxide and nicotine, and five times the amount of tar than cigarettes. Given the low combustibility of the tendu leaf wrapper, bidi smokers must take more frequent and deeper puffs, resulting in the inhalation of more smoke, which is disseminated deeper into the lungs. The decreased NMC detected in bidi smokers may be due to reduced CBF, decline in the number of cilia, and alterations in the viscoelastic properties of mucus.³

The hookah, also known as a shisha or water pipe, is a traditional method of smoking tobacco.^{5,41} Both hookah and cigarette contain nicotine, harmful gases such as carbon monoxide and volatile aldehydes, ultrafine particles, and carcinogenic polycyclic aromatic hydrocarbons (PAHs).^{5,42,43}

After comparing a 45-minute hookah session to smoking a single cigarette, it was found that hookah smokers had higher concentrations of nicotine, carbon monoxide, and PAHs than cigarette smokers.^{5,44} Hookah smoking resulted in increased airway resistance, inflammation, immune cells (neutrophils and lymphocytes), oxidative stress, nitric oxide, and catalase activity in the lungs and NMC of animals.^{5,45,46} In the study by Arıcıgil, the group that used hookahs more than once a week was shown to have impaired NMC. This predisposes them to upper respiratory tract inflammation and injury.⁵

The electronic cigarette (EC) is a device that carries aerosolized nicotine to the respiratory tract.⁶ The EC is marketed as a safer alternative to conventional cigarettes due to its defined composition and noncombustible nature.^{6,36,47} A short-term study investigating the possible side-effects of EC use revealed that EC was safer than cigarettes but had more side-effects than nicotine replacement therapy.⁶ Propylene glycol is the primary ingredient in the majority of EC cartridges on the marketplace today.⁶ Nasal mucociliary clearance in EC smokers was impaired by oxidative stress induced by nicotine exposure via transient receptor potential ankyrin 1 (TRPA 1) receptors.^{6,47} These receptors induce airway surface liquid volume loss and decrease mucus density.^{6,47} Other studies also reported that formaldehyde in ECIG-generated aerosols related to DNA strand breaks and cell death and propylene glycol thicken the respiratory epithelium by increasing the number of goblet cells and increasing the content of mucin within the goblet cell.^{6,36}

Strength and Limitation of the Study

The present systematic review included studies that reported NMC in many types of smoking (cigarette, passive, bidi, hookah, and electronic smoking). In addition, a comprehensive literature search was followed as well as bias protection methods, such as using three independent reviewers.

The limitation of the study was related to the minimal sample of each study and the fact that most of the studies were cross sectional. There were only one randomized controlled trial (RCT) and three prospective studies.

Future Implication

The current systematic review is expected to be a scientific consideration to clinician-related NMC in smokers and general information related the dangers of smoking for the public society. Further research is needed on each component of the NMC for development upon this systematic review.

Final Comments

Our findings suggest that there is an impairment of NMC in smokers. The impairment is not only seen in cigarette smokers but also in passive, bidi, electronic, and hookah smokers. The impairment of NMC in chronic exposure to smoking is caused by the ciliotoxic effect, hypersecretion and viscoelastic change of mucous, airway surface liquid depletion, increased oxidative stress, and deteriorations in the inflammatory and immune systems.

Conflict of Interests

The authors have no conflict of interests to declare.

References

- 1 World Health Organization. WHO global report on trends in prevalence of tobacco smoking 2000–2025, second edition. 2018
- 2 Solak I, Marakoglu K, Pekgor S, Kargin NC, Alatas N, Eryilmaz MA. Nasal mucociliary activity changes in smokers. *Konuralp Tip Derg* 2018;10(03):269–275
- 3 Paul B, Menon SS, Vasthare R, Balakrishnan R, Acharya S. Effect of bidi smoking on nasal mucociliary clearance: a comparative study. *J Laryngol Otol* 2018;132(12):1077–1082
- 4 Dülger S, Akdeniz Ö, Solmaz F, Şengören Dikiş Ö, Yıldız T. Evaluation of nasal mucociliary clearance using saccharin test in smokers: A prospective study. *Clin Respir J* 2018;12(04):1706–1710
- 5 Arıcıgil M, Arbağ H. Hookah smoking impairs nasal mucociliary clearance. *Tob Induc Dis* 2018;16(06):06
- 6 Kumral TL, Saltürk Z, Yildirim G, et al. How does electronic cigarette smoking affect sinonasal symptoms and nasal mucociliary clearance? *B-ENT* 2016;12(01):17–21
- 7 Yadav J, Kaushik G, Ranga RK. Passive smoking affects nasal mucociliary clearance. *JACM* 2014;15(02):96–99
- 8 Kim SY, Sim S, Choi HG. Active and passive smoking impacts on asthma with quantitative and temporal relations: A Korean Community Health Survey. *Sci Rep* 2018;8(01):8614
- 9 Chatkin JM, Dullius CR. The management of asthmatic smokers. *Asthma Res Pract* 2016;2(10):10
- 10 Long M, Fu Z, Li P, Nie Z. Cigarette smoking and the risk of nasopharyngeal carcinoma: a meta-analysis of epidemiological studies. *BMJ Open* 2017;7(10):e016582
- 11 Utiyama DMO, Yoshida CT, Goto DM, et al. The effects of smoking and smoking cessation on nasal mucociliary clearance, mucus properties and inflammation. *Clinics (São Paulo)* 2016;71(06):344–350
- 12 Pagliuca G, Rosato C, Martellucci S, et al. Cytologic and functional alterations of nasal mucosa in smokers: temporary or permanent damage? *Otolaryngol Head Neck Surg* 2015;152(04):740–745
- 13 Alekseenko SI, Skalny AV, Ajsuvakova OP, Skalnaya MG, Notova SV, Tinkov AA. Mucociliary transport as a link between chronic rhinosinusitis and trace element dysbalance. *Med Hypotheses* 2019;127:5–10
- 14 Bustamante-Marin XM, Ostrowski LE. Cilia and mucociliary clearance. *Cold Spring Harb Perspect Biol* 2017;9(04):1–17
- 15 Munkholm M, Mortensen J. Mucociliary clearance: pathophysiological aspects. *Clin Physiol Funct Imaging* 2014;34(03):171–177
- 16 Paul P, Johnson P, Ramaswamy P, Ramadoss S, Geetha B, Subhashini AS. The Effect of ageing on nasal mucociliary clearance in women: A pilot study. *ISRN Pulmonol* 2013;•••:1–5
- 17 Baby MK, Muthu PK, Johnson P, Kannan S. Effect of cigarette smoking on nasal mucociliary clearance: A comparative analysis using saccharin test. *Lung India* 2014;31(01):39–42
- 18 Jiao J, Zhang L. Influence of intranasal drugs on human nasal mucociliary clearance and ciliary beat frequency. *Allergy Asthma Immunol Res* 2019;11(03):306–319
- 19 Jarosław P, Agnieszka P, Jarosław M, et al. Influence of environmental and clinical factors on nasal mucociliary clearance of the students of the medical university of silesia. *Pol Przegląd Otorinolaryngol* 2015;4(02):45–52
- 20 Xavier RF, Ramos D, Ito JT, et al. Effects of cigarette smoking intensity on the mucociliary clearance of active smokers. *Respiration* 2013;86(06):479–485
- 21 Higgins J, Green S. *Cochrane handbook for systematic reviews of intervention* 5.2. United Kingdom: John Wiley and Sons; 2017: 1–50
- 22 Moher D, Liberati A, Tetzlaff J, Altman DG, Group TP; PRISMA Group. Preferred reporting items for systematic reviews and

- meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(07): e1000097
- 23 Herzog R, Álvarez-Pasquin MJ, Díaz C, Del Barrio JL, Estrada JM, Gil Á. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health* 2013;13(154):154
 - 24 Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The newcastle-ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2019
 - 25 Viswanathan M, Ansari MT, Berkman ND, et al. Methods guide for effectiveness and comparative effectiveness reviews, assessing the risk of bias of individual studies in systematic reviews of health care interventions. USA: AHRQ Publication; 2008
 - 26 Islam MM, Iqbal U, Walther B, et al. Benzodiazepine use and risk of dementia in the elderly population: A systematic review and meta-analysis. *Neuroepidemiology* 2016;47(3-4):181-191
 - 27 Luchini C, Stubbs B, Solmi M, Veronese N. Assessing the quality of studies in meta-analyses: Advantages and limitations of the newcastle ottawa scale. *World J Metaanal* 2017;5(04):80-84
 - 28 Nicola ML, Carvalho HB, Yoshida CT, et al. Young "healthy" smokers have functional and inflammatory changes in the nasal and the lower airways. *Chest* 2014;145(05):998-1005
 - 29 Habesoglu TE, Kule M, Kule ZG, et al. How does parental smoking affect nasal mucociliary clearance in children? *Eur Arch Otorhinolaryngol* 2015;272(03):607-611
 - 30 Tamashiro E, Cohen NA, Palmer JN, Lima WT, Lima A. Effects of cigarette smoking on the respiratory epithelium and its role in the pathogenesis of chronic rhinosinusitis. *Rev Bras Otorrinolaringol (Engl Ed)* 2009;75(06):903-907
 - 31 Ramos EM, De Toledo AC, Xavier RF, et al. Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. *Respirology* 2011;16(05):849-855
 - 32 Leopold PL, O'Mahony MJ, Lian XJ, Tilley AE, Harvey BG, Crystal RG. Smoking is associated with shortened airway cilia. *PLoS One* 2009;4(12):e8157
 - 33 Alexander NS, Blount A, Zhang S, et al. CFTR modulation by the tobacco smoke toxin acrolein. *Laryngoscope* 2012;122(06): 1193-1197
 - 34 Cohen NA, Zhang S, Sharp DB, et al. Cigarette smoke condensate inhibits transepithelial chloride transport and ciliary beat frequency. *Laryngoscope* 2009;119(11):2269-2274
 - 35 Proença M, Fagundes Xavier R, Ramos D, Cavalheri V, Pitta F, Cipulo Ramos EM. [Immediate and short term effects of smoking on nasal mucociliary clearance in smokers]. *Rev Port Pneumol* 2011;17(04):172-176
 - 36 Palazzolo DL, Nelson JM, Ely EA, Crow AP, Distin J, Kunigelis SC. The effects of electronic cigarette (ECIG)-generated aerosol and conventional cigarette smoke on the mucociliary transport velocity (MTV) using the bullfrog (*R. catesbiana*) palate paradigm. *Front Physiol* 2017;8(1023):1023
 - 37 Elliott MK, Sisson JH, Wyatt TA. Effects of cigarette smoke and alcohol on ciliated tracheal epithelium and inflammatory cell recruitment. *Am J Respir Cell Mol Biol* 2007;36(04):452-459
 - 38 Habesoglu M, Demir K, Yumusakhuylyu AC, Yilmaz AS, Oysu C. Does passive smoking have an effect on nasal mucociliary clearance? *Otolaryngol Head Neck Surg* 2012;147(01):152-156
 - 39 Duong M, Rangarajan S, Zhang X, et al. Effects of bidi smoking on all-cause mortality and cardiorespiratory outcomes in men from south Asia: an observational community-based substudy of the Prospective Urban Rural Epidemiology Study (PURE). *Lancet Glob Health* 2017;5(02):e168-e176
 - 40 Amith HV, Agrawal D, Gupta A, Shrivastava TP, Purohit BM, Bhambhani G. Assessing the nicotine content of smoked and smokeless forms of Tobacco Available in Bhopal. *Indian J Dent Res* 2018;29(03):341-346
 - 41 Yıldırım F, Çevik Y, Emektar E, Çorbacıoğlu ŞK, Katırcı Y. Evaluating ECG and carboxyhemoglobin changes due to smoking narghile. *Inhal Toxicol* 2016;28(12):546-549
 - 42 Daher N, Saleh R, Jaroudi E, et al. Comparison of carcinogen, carbon monoxide, and ultrafine particle emissions from narghile waterpipe and cigarette smoking: Sidestream smoke measurements and assessment of second-hand smoke emission factors. *Atmos Environ* (1994) 2010;44(01):8-14
 - 43 Shihadeh A, Salman R, Jaroudi E, et al. Does switching to a tobacco-free waterpipe product reduce toxicant intake? A crossover study comparing CO, NO, PAH, volatile aldehydes, "tar" and nicotine yields. *Food Chem Toxicol* 2012;50(05):1494-1498
 - 44 Jacob P III, Abu Raddaha AH, Dempsey D, et al. Nicotine, carbon monoxide, and carcinogen exposure after a single use of a water pipe. *Cancer Epidemiol Biomarkers Prev* 2011;20(11): 2345-2353
 - 45 El-Zaatari ZM, Chami HA, Zaatari GS. Health effects associated with waterpipe smoking. *Tob Control* 2015;24(Suppl 1):i31-i43
 - 46 Nemmar A, Yuvaraju P, Beegam S, John A, Raza H, Ali BH. Cardiovascular effects of nose-only water-pipe smoking exposure in mice. *Am J Physiol Heart Circ Physiol* 2013;305(05):H740-H746
 - 47 Chung S, Baumlin N, Dennis JS, et al. Electronic cigarette vapor with nicotine causes airway mucociliary dysfunction preferentially via TRPA1 receptors. *Am J Respir Crit Care Med* 2019;200(09):1134-1145
 - 48 Uzeloto JS, Ramos D, C F Freire AP, G D Christofaro D, Mara C Ramos E. . Nasal mucociliary transportability of male and female smokers. *Rev Bras Otorrinolaringol (Engl Ed)* 2018;84(03): 311-317