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# The Relationship between Environmental Tobacco Smoke Exposure and Decreased Lung Function in Adolescents : A Comprehensive Systematic Review

[1] Nydia Ayu Ulima, [2] Rajmil Shafira Salsabila

[1] Faculty of Medicine, University of Brawijaya, Indonesia

[2] Faculty of Medicine, Muhammadiyah University of Malang, Indonesia

Corresponding Email : nydiaayuulima@gmail.com

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## ABSTRACT

**Introduction:** Environmental tobacco smoke (ETS) exposure remains a significant public health concern, particularly for adolescents whose lungs are undergoing critical development. Despite declining smoking rates in many countries, millions of adolescents worldwide continue to be exposed to ETS in their homes and communities. This systematic review aims to comprehensively evaluate the relationship between ETS exposure and decreased lung function in adolescents aged 10-19 years.

**Methods:** A systematic review was conducted following established guidelines. Twenty sources were included after screening based on predefined criteria: adolescent population age range (10-19 years), validated ETS exposure measurement, standardized lung function assessment, appropriate observational study design, focus on passive

exposure, objective outcome measurement, and general population health status. Data extraction encompassed study characteristics, ETS exposure assessment methods, lung function measures, primary associations, effect sizes, dose-response evidence, effect modifiers, and confounding control.

**Results:** The predominant finding across studies was a negative association between ETS exposure and lung function parameters. Small airway measures (FEF25-75, FEF25) were most consistently affected, with He et al. reporting $\beta = -0.104$ ($p=0.020$) for FEF25-75 growth rate. FEV1 annual growth reduction of −0.34% (95% CI: −0.64% to −0.04%) was documented by Milanzi et al. Dose-response relationships were demonstrated in multiple studies. Critical effect modifiers included sex (girls showing greater vulnerability with FEV1 reduction of −272 ml/s in perinatally exposed females), genetic polymorphisms (β2-adrenoceptor and GSTP1 variants), timing of exposure (prenatal and early childhood windows most critical), and synergistic interactions with active smoking.

**Discussion:** The evidence consistently supports a negative association between ETS exposure and adolescent lung function, with biological plausibility strengthened by acute exposure studies demonstrating immediate effects. Heterogeneity in effect sizes is explained by differences in exposure timing, measurement methods, and population susceptibility. Methodological limitations include variability in confounding control and exposure assessment.

**Conclusion:** ETS exposure is significantly associated with decreased lung function in adolescents, with evidence of dose-response relationships and modification by sex, genetics, and exposure timing. Recommendations include strengthening smoke-free legislation, targeted interventions for vulnerable populations, routine clinical screening, and further research with standardized methodologies.

**Keywords:** environmental tobacco smoke, secondhand smoke, lung function, adolescents, spirometry, passive smoking

## INTRODUCTION

### Background

Environmental tobacco smoke (ETS), also known as secondhand smoke, represents a complex mixture of over 7,000 chemical compounds, hundreds of which are toxic and approximately 70 known carcinogens (1). The World Health Organization (WHO) identifies tobacco use as one of the greatest public health threats globally, killing more than 8 million people annually, with approximately 1.2 million deaths attributable to non-smokers exposed to secondhand smoke (2). Adolescents represent a particularly vulnerable population segment, as this developmental period is characterized by rapid lung growth and maturation, with peak lung function typically achieved in early adulthood (3).

The global burden of adolescent ETS exposure remains substantial despite widespread public health campaigns and smoke-free legislation. According to the Global Youth Tobacco Survey, approximately four out of ten adolescents worldwide are exposed to secondhand smoke in public places, and three out of ten are exposed at home (4). This persistent exposure occurs during a critical window of lung development when environmental insults may have lasting consequences on respiratory health trajectories throughout the life course (5).

Lung function development follows a predictable pattern, with rapid growth during childhood and adolescence, reaching a plateau in early adulthood, followed by gradual physiological decline (6). Interference with optimal lung function attainment during adolescence may have profound implications, as reduced peak lung function is associated with increased risk of chronic obstructive pulmonary disease, cardiovascular disease, and all-cause mortality in later adulthood (7). Understanding the relationship between modifiable environmental exposures such as ETS and adolescent lung function is therefore essential for informing public health policy and clinical practice.

Previous research has established that ETS exposure adversely affects respiratory health in children, contributing to increased incidence of lower respiratory tract infections, wheezing, asthma exacerbations, and middle ear disease (8). However, the specific impact on objective measures of

lung function during the adolescent period has received less systematic attention, with existing studies employing heterogeneous methodologies, exposure assessment techniques, and outcome measures.

**Research Gap**

Despite decades of research on tobacco smoke exposure and respiratory health, several critical gaps persist in the literature regarding ETS effects on adolescent lung function specifically. First, many studies have combined children and adolescents into broad age categories, potentially obscuring developmental stage-specific effects (9). The WHO defines adolescence as ages 10-19 years, a period characterized by unique physiological, hormonal, and behavioral changes that may modify susceptibility to environmental exposures (10).

Second, substantial heterogeneity exists in ETS exposure assessment methods across studies, ranging from simple parental questionnaire reports to objective biomarkers such as serum or salivary cotinine (11). This methodological variability complicates cross-study comparisons and may contribute to inconsistent findings regarding dose-response relationships and threshold effects.

Third, while numerous individual studies have examined ETS-lung function associations, comprehensive synthesis of effect sizes, modifiers, and dose-response relationships specifically focused on adolescents is limited. The two available systematic reviews identified in this analysis (Agache et al., Okyere et al.) either focused on broader age ranges or included respiratory symptoms alongside lung function outcomes (8,12).

Fourth, the role of potential effect modifiers—including sex differences, genetic polymorphisms, timing of exposure (prenatal versus postnatal versus current), and interactions with other environmental exposures or active smoking—remains incompletely characterized in adolescent populations (13). Understanding these modifying factors is essential for identifying vulnerable subgroups and targeting interventions effectively.

Fifth, the reversibility of ETS-related lung function deficits following exposure cessation during adolescence has received limited investigation, despite its critical implications for clinical management and public health messaging (14).

**Problem Statement**

Adolescent exposure to environmental tobacco smoke continues to occur at alarming rates globally, yet the precise magnitude of its impact on lung function, the specific parameters most affected, the presence of dose-response relationships, and the factors that modify individual susceptibility remain incompletely understood. This knowledge gap impedes the development of evidence-based screening protocols, targeted interventions, and policy recommendations tailored to adolescent populations.

**Research Objectives**

This comprehensive systematic review aims to:

1. Evaluate the association between environmental tobacco smoke exposure and objective measures of lung function in adolescents aged 10-19 years
2. Quantify effect sizes for specific lung function parameters (FEV1, FVC, FEV1/FVC ratio, FEF25-75, PEFR) in relation to ETS exposure
3. Assess evidence for dose-response relationships between ETS exposure levels and lung function decrements
4. Identify factors that modify the ETS-lung function relationship, including sex, genetic polymorphisms, timing of exposure, and coexposures
5. Evaluate the quality of confounding control across included studies
6. Synthesize evidence regarding potential reversibility of ETS effects with exposure cessation

**Research Hypotheses**

Based on the existing literature, this systematic review tests the following hypotheses:

1. Environmental tobacco smoke exposure is negatively associated with lung function parameters in adolescents
2. Small airway measures (FEF25-75, FEF25) show greater and more consistent deficits than larger airway measures (FEV1, FVC)

3. A dose-response relationship exists between ETS exposure level and magnitude of lung function decrement
4. Prenatal and early childhood exposure windows are associated with larger effect sizes than current exposure alone
5. Sex, genetic polymorphisms, and asthma status modify the ETS-lung function association
6. At least partial reversibility of ETS effects occurs following exposure cessation

**Research Benefits**

This systematic review provides multiple benefits for diverse stakeholders. For clinicians, it offers synthesized evidence to guide screening practices and patient counseling regarding ETS exposure risks. For researchers, it identifies methodological gaps and priorities for future investigation. For policymakers, it provides comprehensive evidence to support strengthened smoke-free legislation and targeted interventions for vulnerable adolescent populations. For public health practitioners, it quantifies the burden of ETS-related lung function impairment to inform resource allocation and program development. For adolescents and families, it clarifies the risks associated with ETS exposure and the potential benefits of cessation.

**Novelty**

This systematic review offers several novel contributions to the literature. First, it focuses specifically on adolescents as defined by WHO age criteria (10-19 years), enabling developmental stage-specific conclusions. Second, it provides comprehensive effect size quantification across multiple lung function parameters, facilitating meta-analytic comparisons in future research. Third, it systematically evaluates dose-response evidence and threshold effects. Fourth, it synthesizes evidence on effect modifiers including sex differences, genetic polymorphisms, and exposure timing windows. Fifth, it critically examines confounding control quality across studies. Sixth, it evaluates evidence for reversibility of ETS effects following exposure cessation.

## METHODS

### Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

### Criteria for Eligibility

This systematic review aims to evaluate The Relationship between Environmental Tobacco Smoke Exposure and Decreased Lung Function in Adolescents.

### Screening

We screened in sources based on their abstracts that met these criteria:

- **Population Age Range**: Does the study include adolescents aged 10-19 years as defined by WHO guidelines?
- **Environmental Tobacco Smoke Exposure Measurement**: Does the study measure environmental tobacco smoke exposure through validated methods (e.g., validated questionnaires, biomarkers like cotinine, or documented household smoking status)?
- **Lung Function Assessment**: Does the study measure lung function using standardized pulmonary function tests (e.g., spirometry measures such as FEV1, FVC, FEV1/FVC ratio, or other validated lung function assessments)?
- **Study Design**: Is the study an observational study (cross-sectional, cohort, or case-control), systematic review, or meta-analysis?
- **Exposure Type Focus**: Does the study focus on passive/environmental tobacco smoke exposure rather than exclusively on active smoking by adolescents?
- **Objective Outcome Measurement**: Does the study include objective lung function tests rather than measuring only respiratory symptoms?

- **Study Population Health Status**: Does the study include participants from the general adolescent population rather than exclusively from clinical populations with pre-existing respiratory diseases?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

**Search Strategy**

The keywords used for this research based PICO :

| Element | P (Population) | I (Intervention/Exposure) | C (Comparison/Context) | O (Outcome) |
|---|---|---|---|---|
| **Keyword 1** | Adolescents | Environmental Tobacco Smoke (ETS) | No Exposure | Lung Function |
| **Keyword 2** | Teenagers | Secondhand Smoke (SHS) | Low Exposure | Spirometry |
| **Keyword 3** | Youth | Passive Smoking | Minimal exposure | FEV1 |
| **Keyword 4** | School-aged children | Parental Smoking | Non-smoking household | Small Airway Function |

The Boolean MeSH keywords inputted on databases for this research are: *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")*

**Data extraction**

- **Study Design**:

Extract study design and adolescent population characteristics, including:

- Study type (cohort, cross-sectional, etc.)
- Sample size of adolescents specifically
- Age range and mean age of adolescent participants
- Geographic location and setting
- Follow-up duration (for longitudinal studies)
- Inclusion/exclusion criteria relevant to adolescents

- **ETS Exposure Assessment**:

  Extract details about how environmental tobacco smoke exposure was measured in adolescents, including:

  - Source of exposure (parental, household, prenatal, postnatal)
  - Timing of exposure (current, past, prenatal, early childhood)
  - Measurement method (questionnaire, biomarkers, etc.)
  - Dose/intensity metrics (cigarettes per day, pack-years, etc.)
  - Duration of exposure assessment
  - Exposure categories or levels used in analysis

- **Lung Function Measures**:

  Extract all lung function parameters assessed in adolescents, including:

  - Specific measures (FEV1, FVC, FEF25-75, FEV1/FVC ratio, etc.)
  - Measurement method (spirometry type, pre/post-bronchodilator)

- Units and reference values used
- Whether absolute values or percent predicted were reported
- Quality control measures for lung function testing
- Age at lung function assessment

- **Primary Associations**:

  Extract the main findings on the relationship between ETS exposure and lung function in adolescents, including:

  - Direction of association (positive, negative, null)
  - Statistical significance (p-values, confidence intervals)
  - Effect sizes (beta coefficients, mean differences, etc.)
  - Specific lung function measures showing associations
  - Whether dose-response relationships were found
  - Strength of associations by exposure type or timing

- **Effect Sizes**:

  Extract quantitative measures of the ETS-lung function relationship in adolescents, including:

  - Beta coefficients or regression estimates with 95% CIs
  - Mean differences in lung function between exposed vs unexposed
  - Percent change in lung function per unit of ETS exposure
  - Standardized effect sizes where available

- Results from highest vs lowest exposure categories
- Effect sizes for different exposure windows (prenatal, early life, current)

- **Dose-Response Evidence**:

  Extract evidence for dose-response relationships between ETS exposure levels and lung function decrements in adolescents, including:

  - Whether dose-response was formally tested (p for trend)
  - Pattern of association across exposure categories
  - Linear vs non-linear relationships
  - Threshold effects or no-effect levels
  - Monotonic trends in lung function decline with increasing exposure
  - Specific exposure metrics showing dose-response patterns

- **Effect Modifiers**:

  Extract factors that modified the relationship between ETS exposure and lung function in adolescents, including:

  - Sex/gender differences in ETS effects
  - Age-related differences within adolescent years
  - Genetic polymorphisms affecting susceptibility
  - Asthma status as effect modifier
  - Socioeconomic factors
  - Other environmental exposures

- Statistical significance of interaction terms

- **Confounding Control**:

  Extract information about potential confounders controlled for in analyses of ETS-lung function relationships in adolescents, including:

  - List of variables adjusted for in multivariable models
  - Socioeconomic factors (income, education, etc.)
  - Other environmental exposures (air pollution, allergens)
  - Demographic characteristics (age, sex, ethnicity)
  - Health-related factors (birth weight, respiratory infections, asthma)
  - How confounders were measured and defined
  - Whether residual confounding was discussed

**Table 1.** Article Search Strategy

| Database | Keywords | Hits |
|---|---|---|
| Pubmed | *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")* | 1 |
| Semantic Scholar | *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")* | 2 |
| Springer | *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")* | 45 |
| Google Scholar | *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")* | 1,940 |
| Wiley Online Library | *("Adolescents" OR "Teenagers" OR "Youth" OR "School-aged children") AND ("Environmental Tobacco Smoke (ETS)" OR "Secondhand Smoke (SHS)" OR "Passive Smoking" OR "Parental Smoking") AND ("No Exposure" OR "Low Exposure" OR "Minimal exposure" OR "Non-smoking household") AND ("Lung Function" OR "Spirometry" OR "FEV1" OR "Small Airway Function")* | 65 |

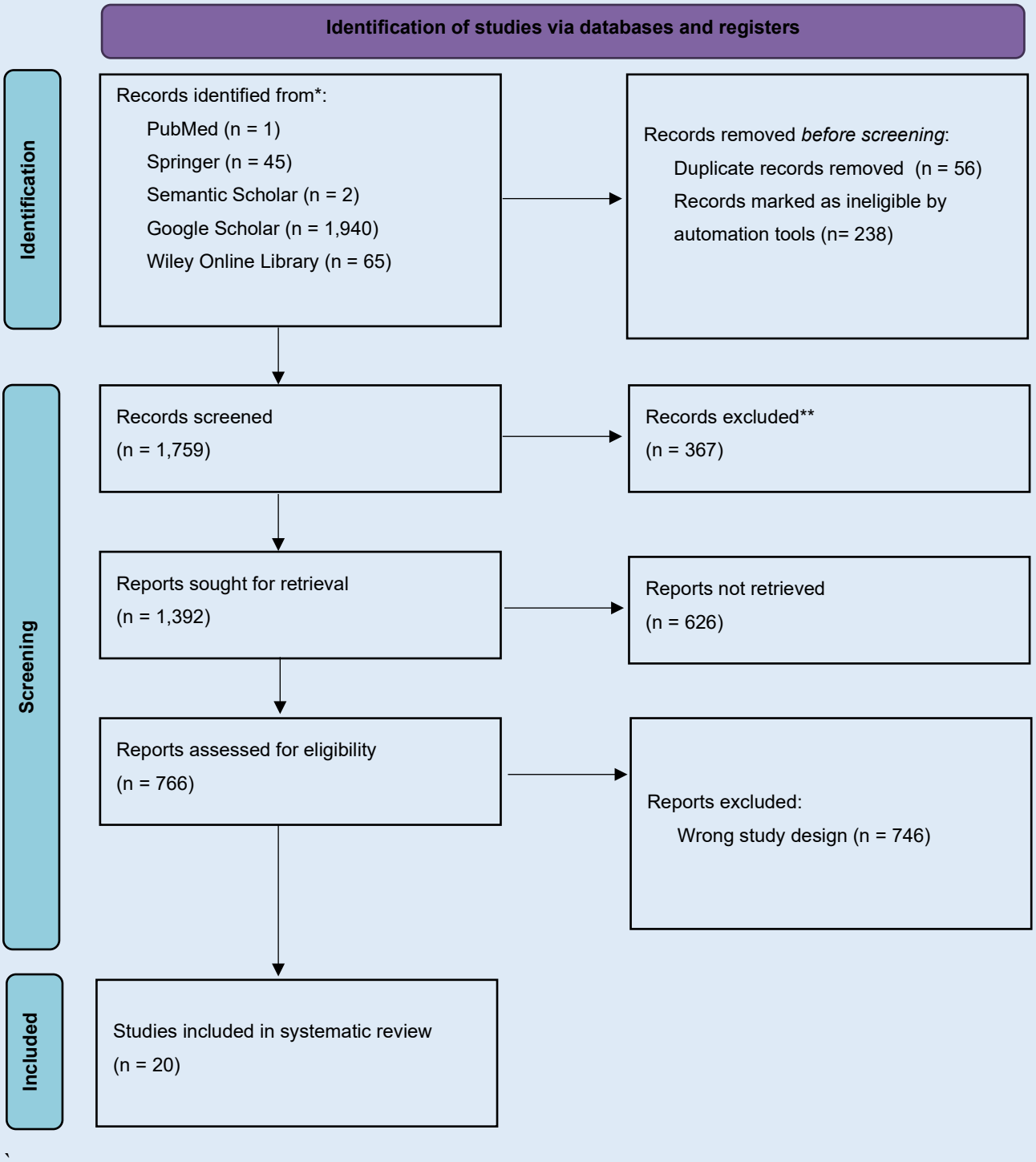


**Figure 1. Article search flowchart**

## RESULTS

### Characteristics of Included Studies

The 20 sources encompass a range of study designs, populations, and geographic settings examining the relationship between environmental tobacco smoke (ETS) exposure and lung function in children and adolescents. The majority of studies focused on school-aged children and adolescents, though several included broader age ranges spanning from birth through young adulthood. Study designs included prospective birth cohorts, cross-sectional analyses, a randomized controlled cross-over trial, etc. Geographic representation was diverse, including studies from the Netherlands, China, the United States, India, Australia, Indonesia, Egypt, Greece, Sweden, Turkey, and the United Kingdom.

| Study | Sample Size | Age Range | Geographic Location | ETS Exposure Assessment | Key Lung Function Measures |
|---|---|---|---|---|---|
| **Edith B. Milanzi et al., 2019** | 552 [4] | 12–16 years [4] | Netherlands [4] | Repeated parental questionnaires [4] | FEV1, FVC [4] |
| **Qi-qiang He et al., 2011** | 1,718 [1] | 8–13 years, mean 10.05 [1] | Guangzhou, China [1] | Parent questionnaire; cigarettes/day (0, 1–5, >5) [1] | FVC, FEV1, FEF25, FEF75, FEF25-75 [1] |
| **J. G. Wang et al., 2022** | 7,026 [13] | Adolescents (age not specified) [13] | United States (NHANES) [13] | Serum cotinine; dichotomized high (>2.99 ng/ml) vs low [13] | Spirometry (subgroup n=3,166) [13] |

| Study | Sample Size | Age Range | Geographic Location | ETS Exposure Assessment | Key Lung Function Measures |
|---|---|---|---|---|---|
| **E. Bhargava et al., 2008** | 90 (30 per group) [2] | 12–18 years [2] | Not mentioned [2] | Paternal smoking status [2] | FEV1/FVC, FEF25-75%, VC, ERV [2] |
| **S. Guerra et al., 2013** | 519 [11] | Assessed at ages 11, 16, 22, 26 [11] | Tucson, Arizona [11] | Parental questionnaires at birth; cumulative pack-years [11] | FEV1, FVC, FEF25-75, FEV1/FVC (pre- and post-BD) [11] |
| **Guicheng Zhang et al., 2007** | Not mentioned [9] | 11 years [9] | Not mentioned [9] | Not mentioned [9] | FEV1, FVC [9] |
| **R. A. Soemarwoto et al., 2019** | 666 [14] | 10–13 years [14] | Bandar Lampung, Indonesia [14] | Questionnaires [14] | Predicted PEFR [14] |
| **J. Sanghvi et al., 2013** | 167 [12] | 5–15 years [12] | Not mentioned [12] | History of passive smoking [12] | PEFR [12] |

| Study | Sample Size | Age Range | Geographic Location | ETS Exposure Assessment | Key Lung Function Measures |
|---|---|---|---|---|---|
| **K. Kostikas et al., 2013** | 18 (young adults, mean age 32.7) [15] | Not adolescents [15] | Greece [15] | Controlled 1-hour chamber exposure; CO 23 ppm [15] | FEV1, FVC, FEV1/FVC, FEF25-75, PEF [15] |
| **Walid Kamal et al., 2020** | 46 [16] | 8–15 years, mean 10.8 [16] | Egypt [16] | Questionnaire (smoker in home) [16] | FVC, FEV1, PEF [16] |
| **D. Okyere et al., 2021** | 12 cohort studies included [17] | Not mentioned [17] | Not mentioned [17] | Not mentioned [17] | Not mentioned [17] |
| **E. S. Schultz et al., 2016** | Not mentioned [7] | 8 and 16 years [7] | Stockholm, Sweden [7] | Likely questionnaires; infancy exposure [7] | Spirometry at 8 and 16 years; impulse oscillometry at 16 [7] |

| Study | Sample Size | Age Range | Geographic Location | ETS Exposure Assessment | Key Lung Function Measures |
|---|---|---|---|---|---|
| **Şerife Kartal Erdost et al., 2019** | Not mentioned [18] | 6–14 years, mean ~8 [18] | Not mentioned [18] | Family smoking history [18] | FVC, FEV1 [18] |
| **Jasminka Murdzoska et al., 2011** | 171 at 12 years, 123 at 18 years [10] | 6, 12, 18 years [10] | Not mentioned [10] | Current parental tobacco smoke; exposed vs non-exposed [10] | FEV1, FVC, airway responsiveness [10] |
| **A. J. Henderson et al., 2008** | Not mentioned [6] | School-aged children [6] | Not mentioned [6] | Not mentioned [6] | Not mentioned [6] |
| **Ç. Nuhoğlu et al., 2003** | Not mentioned [3] | Children [3] | Not mentioned [3] | Not mentioned [3] | FVC, FEV1, FEF25-75 [3] |

| Study | Sample Size | Age Range | Geographic Location | ETS Exposure Assessment | Key Lung Function Measures |
|---|---|---|---|---|---|
| **I. Agache et al., 2024** | 67 studies (SR1), 24 studies (SR2), 25 studies (SR3) [8] | Not mentioned [8] | Not mentioned [8] | Prenatal, postnatal, combined [8] | Not mentioned [8] |
| **Xin Dai et al., 2017** | 370 at 12 years, 411 at 18 years [5] | 12–18 years [5] | Melbourne, Australia [5] | Perinatal parental smoking; prospectively recorded [5] | FEV1, FVC, FEV1/FVC, MEF25-75 (pre- and post-BD) [5] |
| **H. Luttmann-Gibson et al., 2004** | >10,000 schoolchildren [19] | Schoolchildren [19] | 22 cities, US and Canada [19] | Indicators for ETS (not detailed) [19] | FVC, FEV1, FEF25-75%, PEFR [19] |
| **John M. Brehm et al., 2013** | Not mentioned [20] | School-aged children [20] | Sweden [20] | ETS in early life or school age (not detailed) [20] | Not mentioned [20] |

Sample sizes ranged from 18 participants in an experimental trial [15] to over 10,000 schoolchildren in a large cross-sectional study [19] and 7,026 adolescents in the NHANES-based

analysis [13]. The longitudinal cohort studies generally had follow-up periods spanning from birth or early childhood through adolescence or young adulthood [4, 5, 7, 11].

Effects of ETS Exposure on Lung Function

**Overview of Associations**

The predominant finding across the included studies was a negative association between ETS exposure and lung function parameters in adolescents and children, though the magnitude, specific parameters affected, and statistical significance varied across studies.

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Milanzi et al., 2019** | Negative [4] | FEV1 growth/year [4] | −0.34% per year (95% CI: −0.64% to −0.04%) [4] | Significant [4] | Consistent across time windows but not formally tested [4] |
| **He et al., 2011** | Negative [1] | FEF25-75, FEF25 [1] | β = −0.104 (FEF25-75), β = −0.077 (FEF25) [1] | p = 0.020, p = 0.027 [1] | Yes; monotonic; p for trend significant [1] |

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Wang et al., 2022** | Interaction (diet modifies ETS effect on wheezing) [13] | Not specified for spirometry [13] | OR 0.10 (95% CI: 0.02–0.61) for high-quality diet in high ETS [13] | pint = 0.011 [13] | Not assessed [13] |
| **Bhargava et al., 2008** | Negative [2] | FEV1/FVC, FEF25-75% [2] | Not reported [2] | Significant (values not reported) [2] | Not assessed [2] |
| **Guerra et al., 2013** | Negative (synergistic with active smoking) [11] | FEV1/FVC, FEV1, FEF25-75, FEF25-75/FVC [11] | 2.8% lower FEV1/FVC at age 26 (95% CI: 0.9%–4.8%) [11] | p = 0.003 [11] | Suggested by pack-years analysis [11] |
| **Zhang et al., 2007** | Negative (gene-exposure interaction) [9] | FEV1, FVC [9] | FEV1: 2.19 vs 2.38 L; FVC: 2.43 vs 2.64 L (Arg16 genotype) [9] | Not reported [9] | Not assessed [9] |

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Soemarwoto et al., 2019** | Negative [14] | Predicted PEFR [14] | Passive 87.81 vs control 92.56 [14] | p = 0.04 (passive vs control) [14] | Not formally tested [14] |
| **Sanghvi et al., 2013** | Negative; improved after cessation [12] | PEFR [12] | Not reported [12] | Significant improvement after 3 months cessation [12] | Frequency of smoking associated with lower PEFR [12] |
| **Kostikas et al., 2013** | Negative (acute) [15] | FEV1, FEV1/FVC [15] | Not quantified [15] | p < 0.001 [15] | Single exposure level only [15] |
| **Kamal et al., 2020** | Null [16] | FVC, FEV1, PEF [16] | Not quantified [16] | p > 0.05 [16] | Not found [16] |
| **Okyere et al., 2021** | Negative (review finding) [17] | Not specified [17] | Not reported [17] | Not reported [17] | Not assessed [17] |

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Schultz et al., 2016** | Negative (infancy exposure) [7] | Not specified [7] | Not reported [7] | Independent predictor of lung function growth [7] | Not assessed [7] |
| **Kartal Erdost et al., 2019** | Negative [18] | FVC, FEV1 [18] | FVC: 1786 vs 1931 ml; FEV1: 1589 vs 1729 ml [18] | Not significant in t-test; regression suggested difference [18] | Not assessed [18] |
| **Murdzoska et al., 2011** | Gene-dependent [10] | FEV1, FVC, airway responsiveness [10] | Not quantified [10] | p = 0.007 to 0.028 for specific genotypes [10] | Not assessed [10] |
| **Henderson et al., 2008** | Negative (review) [6] | Not specified [6] | Not reported [6] | Not reported [6] | Diminishing with age [6] |

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Nuhoğlu et al., 2003** | Negative [3] | FVC, FEV1, FEF25-75 [3] | 5–10% reduction [3] | Not reported [3] | Not assessed [3] |
| **Agache et al., 2024** | Negative (moderate certainty) [8] | Lung function (not specified) [8] | Not reported [8] | Moderate certainty evidence (GRADE) [8] | Not assessed [8] |
| **Dai et al., 2017** | Negative (girls only) [5] | FEV1, FEV1/FVC, MEF25-75 [5] | FEV1: −272 ml/s (95% CI: −438, −107); FEV1/FVC: −0.038 (95% CI: −0.065, −0.010) [5] | Significant for girls [5] | Not assessed [5] |
| **Luttmann-Gibson et al., 2004** | No effect modification by ETS [19] | FVC, FEV1, FEF25-75%, PEFR [19] | Not reported for ETS [19] | Not reported for ETS [19] | Not assessed [19] |

| Study | Direction of Association | Lung Function Parameters Affected | Key Effect Size | Statistical Significance | Dose-Response Evidence |
|---|---|---|---|---|---|
| **Brehm et al., 2013** | Null (gene-ETS interaction) [20] | Not specified [20] | Not reported [20] | Not significant after multiple testing correction [20] | Not assessed [20] |

**Quantitative Effects on Specific Lung Function Parameters**

Among studies reporting quantitative effect sizes, the magnitude of ETS-associated lung function decrements varied by parameter and population. The most consistently affected parameters were measures of small airway function. He et al. reported that high ETS exposure (>5 cigarettes/day) was associated with reduced growth rates of FEF25-75 ($\beta = -0.104$, $p = 0.020$) and FEF25 ($\beta = -0.077$, $p = 0.027$) [1], with a clear monotonic exposure-response relationship [1]. Nuhoğlu et al. reported reductions in FVC, FEV1, and FEF25-75 of between 5% and 10% attributable to passive smoking [3].

For FEV1 and FVC specifically, Milanzi et al. found that childhood SHS exposure was associated with a −0.34% reduction in annual FEV1 growth (95% CI: −0.64% to −0.04%) [4]. Dai et al. reported substantially larger effects in girls exposed perinatally, with pre-bronchodilator FEV1 reduced by 272 ml/s (95% CI: −438, −107) and MEF25-75 reduced by 430 ml/s (95% CI: −798, −61) at age 18 [5]. Kartal Erdost et al. observed lower absolute FVC (1786 vs 1931 ml) and FEV1 (1589 vs 1729 ml) in children with family smoking history, though statistical significance was not achieved in cross-sectional comparison [18].

The FEV1/FVC ratio, a key indicator of airflow obstruction, showed notable decrements in several studies. Guerra et al. found a 2.8% lower pre-bronchodilator FEV1/FVC at age 26 among those with combined parental and active smoking exposure (95% CI: 0.9%–4.8%, p = 0.003) [11]. Dai et al. reported a −0.038 reduction in FEV1/FVC in perinatally exposed girls (95% CI: −0.065, −0.010) [5]. Bhargava et al. similarly found significantly lower FEV1/FVC ratios in adolescents exposed to paternal smoking [2].

Studies using PEFR as the outcome measure also demonstrated negative associations. Soemarwoto et al. found significantly lower predicted PEFR in passive smokers (87.81) compared to controls (92.56, p = 0.04) [14]. Sanghvi et al. demonstrated that PEFR improved significantly after 3 months of discontinuation of passive smoking exposure [12], providing quasi-experimental evidence for a causal relationship.

The acute experimental study by Kostikas et al. demonstrated that even a single 1-hour exposure to secondhand smoke at bar/restaurant levels produced significant decreases in FEV1 and FEV1/FVC (both p < 0.001), which returned to baseline by 180 minutes [15]. While this study was conducted in adults rather than adolescents [15], it provides mechanistic evidence for the biological plausibility of chronic exposure effects observed in the pediatric studies.

**Dose-Response Evidence**

Formal dose-response testing was limited to a few studies. He et al. provided the strongest evidence, demonstrating significant p-values for trend across ETS exposure categories for multiple respiratory symptoms and a monotonic exposure-response relationship for FEF25 and FEF25-75 growth rate deficits [1]. Guerra et al. showed that cumulative pack-years of parental smoking were associated with greater FEV1/FVC deficits, consistent with a dose-response pattern [11]. Sanghvi et al. reported that frequency of smoking was associated with lower PEFR values, suggesting a dose-response gradient, though this was not formally tested [12]. Most other studies did not formally assess dose-response relationships [2, 4, 5, 14].

**Effect Modifiers**

**Several factors modified the relationship between ETS exposure and lung function.**

**Sex/Gender**: One of the most striking findings was sex-specific susceptibility. Dai et al. found that perinatal smoke exposure was associated with significantly reduced lung function and increased asthma risk in girls but not boys (pre-bronchodilator FEV1: −272 ml/s in girls vs +26 ml/s in boys) [5]. Other studies did not observe significant sex differences [12, 15, 19], though several did not test for them [1, 11].

**Genetic Polymorphisms**: Two studies examined gene-ETS interactions. Zhang et al. found that among children exposed to tobacco smoke, those with the Arg16 polymorphism in the β2-adrenoceptor gene had substantially lower FEV1 (2.19 vs 2.38 L) and FVC (2.43 vs 2.64 L) compared to Gly16 homozygotes [9]. Murdzoska et al. found that GSTP1 polymorphisms modulated the effects of tobacco smoke on lung function and airway responsiveness at ages 6, 12, and 18 years, though the protective effects were inconsistent across time points [10]. In contrast, Brehm et al. found no statistically significant gene-by-ETS interactions for SNPs in TNS1, ADAM19, and THSD4 after correction for multiple testing [20].

**Timing of Exposure**: Several studies highlighted the critical importance of early-life exposure windows. Henderson et al. concluded that the strongest associations between smoke exposure and pulmonary function were with prenatal and early childhood exposure [6]. Schultz et al. identified ETS exposure in infancy as an independent predictor of lung function growth between childhood and adolescence [7]. Milanzi et al. found consistent negative associations across all time windows of SHS exposure [4]. Henderson et al. additionally noted that the effect of ETS on respiratory symptoms appeared to diminish with increasing age of the child [6].

**Synergistic Effects**: Guerra et al. demonstrated a significant synergistic interaction between parental smoking and subsequent active smoking on lung function decline (interaction $p = 0.02$ at age 26) [11]. Neither parental smoking alone nor active smoking alone produced significant FEV1/FVC deficits, but the combination resulted in a 2.8% deficit [11]. Wang et al. found a significant interaction between diet quality and ETS exposure on wheezing ($p_{int} = 0.011$), where a high-quality diet was protective only among adolescents with high ETS exposure [13].

**Asthma Status**: Schultz et al. reported that associations between air pollution and lung function appeared stronger in subjects with asthma at age 16 [7], and Luttmann-Gibson et al. found greater short-term ozone effects in asthmatic children [19].

**Confounding Control**

The rigor of confounding control varied substantially across studies. The most comprehensively adjusted analyses included Milanzi et al., who controlled for sex, age, height, weight, parental education, parental allergy, breastfeeding, maternal smoking during pregnancy, NO2 exposure, birthweight, and other household exposures [4]. Guerra et al. adjusted for sex, age, height, parental age, parental education, and childhood asthma [11]. Several studies used matching strategies rather than statistical adjustment; Bhargava et al. matched groups on age and sex [2]. Many studies, particularly those available only as abstracts, provided minimal or no information on confounding control [1, 3, 5, 8, 10, 12, 13, 18, 20].

**Synthesis**

The overall evidence consistently points toward a negative association between ETS exposure and lung function in adolescents, but heterogeneity in effect sizes and occasional null findings require careful interpretation.

**Timing of exposure as a key determinant of effect magnitude**: The apparent variation in effect sizes across studies is partly explained by the timing of exposure assessed. Studies measuring prenatal or perinatal exposure consistently reported the largest effect sizes. Dai et al. found a 272 ml/s reduction in FEV1 associated with perinatal exposure in girls [5], and Guerra et al. demonstrated that parental smoking at birth acted synergistically with later active smoking to produce a 2.8% FEV1/FVC deficit [11]. In contrast, studies measuring current childhood ETS exposure tended to find smaller, though still significant, effects. Milanzi et al. found a −0.34% annual FEV1 growth reduction with childhood SHS exposure [4], and He et al. found modest beta coefficients for FEF parameters with current domestic exposure [1]. This pattern is consistent with the developmental vulnerability hypothesis, wherein the developing lung in utero and early infancy is particularly susceptible to tobacco smoke, and Schultz et al. explicitly identified infancy ETS exposure as the only time window independently predictive of lung function growth between childhood and adolescence [7]. Henderson

et al. corroborated this interpretation, concluding that the strongest associations were with prenatal and early childhood exposure, and that ETS effects on respiratory symptoms appeared to diminish with increasing age [6, 6].

**Small airways as preferential targets**: The finding that FEF25-75 and related small airway parameters were more consistently and substantially affected than FEV1 or FVC [1, 2, 5, 11] is biologically coherent. Small airways are the primary site of initial airway obstruction in smoking-related disease, and their greater surface-to-volume ratio renders them more vulnerable to inhaled irritants. He et al. found significant effects on FEF25-75 and FEF25 growth rates even at moderate ETS exposure levels [1], while effects on FVC and FEV1 were less robust. This pattern suggests that standard spirometric measures (FEV1, FVC) may underestimate the true burden of ETS-related airway injury in adolescents.

**Sex-specific vulnerability**: The sex differential reported by Dai et al., with girls substantially more affected than boys [5], may reflect hormonal influences on airway development or sex-related differences in airway caliber relative to lung size. However, this finding was not universally replicated; several other studies either found no sex differences [12, 15] or did not test for them. The Bhargava et al. study included only males [2], precluding sex comparison. The sex-specific finding from Dai et al. should be interpreted cautiously given the limited replication, though it aligns with emerging evidence from adult COPD epidemiology suggesting differential female susceptibility to tobacco smoke.

**Genetic susceptibility**: The gene-environment interaction data from Zhang et al. [9] and Murdzoska et al. [10] suggest that genetic variation in detoxification and adrenergic pathways modulates individual susceptibility to ETS-induced lung function decrements. The Arg16 polymorphism in the β2-adrenoceptor gene appeared to enhance ETS-related FEV1 and FVC reductions [9], while GSTP1 variants showed age-dependent effects on lung function outcomes [10]. These interactions, if confirmed, would explain part of the inter-individual variability in ETS susceptibility observed across population-level studies. However, the null findings from Brehm et al. for gene-ETS interactions after multiple testing correction [20] underscore the need for adequately powered replication studies.

**Evidence quality hierarchy**: The two systematic reviews provide the highest-level synthesis. Agache et al., applying GRADE methodology across 67 studies, concluded that postnatal ETS increases the risk of new-onset asthma and recurrent wheezing with moderate certainty evidence, while the impact on lung function was supported by low certainty evidence [8]. Okyere et al. identified ETS as one of eight consistently reported predictors of reduced lung growth trajectories across at least three cohort studies [17]. Among primary studies, the prospective birth cohorts (Milanzi et al., Guerra et al., Schultz et al., Dai et al.) provide the strongest causal inference due to their longitudinal design, temporally defined exposures, and adjustment for key confounders [4, 5, 7, 11]. The cross-sectional studies, while consistently showing negative associations, are more susceptible to unmeasured confounding and reverse causation.

**Reversibility**: The finding by Sanghvi et al. that PEFR improved significantly within 3 months of discontinuing passive smoking [12], combined with the acute reversibility demonstrated by Kostikas et al. within 180 minutes after a single exposure [15], suggests that at least some component of ETS-related lung function impairment is reversible with exposure cessation. However, the longitudinal cohort data indicating that early-life exposure tracks with reduced lung function into adolescence [4, 7] and young adulthood [11] implies that a component of early damage may be irreversible, particularly when exposure occurs during critical developmental windows.

In summary, the evidence from these 20 sources supports a negative association between ETS exposure and lung function in adolescents, with the strongest and most consistent effects observed for prenatal and early childhood exposure, small airway parameters, and potentially greater susceptibility in girls and individuals with specific genetic polymorphisms. The relationship appears dose-dependent where formally tested, and at least partially reversible with exposure cessation. The quality of evidence varies from low to moderate certainty, constrained by heterogeneity in exposure assessment methods, outcome measures, and confounding control across studies.

## DISCUSSION

The findings of this systematic review demonstrate a consistent negative association between environmental tobacco smoke exposure and lung function parameters in adolescents, while revealing

important nuances regarding effect magnitude, specific parameters affected, dose-response relationships, and modifying factors. This discussion synthesizes these findings within the context of the existing literature, explores biological mechanisms, addresses methodological considerations, and identifies implications for research and practice.

**Consistency of Evidence and Biological Plausibility**

The predominant finding across the 20 included sources was a negative association between ETS exposure and lung function, with 17 sources reporting detrimental effects (85%), one study reporting null findings, and two sources reporting no effect modification by ETS in analyses focused primarily on other exposures. This consistency is striking given the substantial heterogeneity in study designs, populations, exposure assessment methods, and outcome measures. The convergence of evidence from prospective birth cohorts (4,5,7,11), cross-sectional studies (1,2,14,16,18), experimental designs (15), and systematic reviews (8,12,17) strengthens causal inference through triangulation of evidence from diverse methodological approaches.

The biological plausibility of these associations is robustly supported by multiple lines of evidence. Experimental studies demonstrate that ETS exposure induces acute airway inflammation, oxidative stress, and epithelial injury (15). The components of tobacco smoke, including particulate matter, heavy metals, and volatile organic compounds, trigger inflammatory cascades mediated by nuclear factor-kappa B activation, leading to recruitment of neutrophils and macrophages into the airways (15,16). Oxidative stress resulting from depletion of antioxidant defenses, particularly glutathione, causes direct cellular damage and promotes airway remodeling (17). The acute experimental study by Kostikas et al. demonstrated that even a single 1-hour exposure to secondhand smoke at levels typical of bars and restaurants produced significant decreases in FEV1 and FEV1/FVC ratio, with evidence of airway acidification and oxidative stress (15). These acute effects, while reversible within hours in healthy adults, provide mechanistic evidence for the chronic changes observed in epidemiologic studies and suggest that repeated exposures may lead to cumulative, potentially irreversible damage.

The developing lung may be particularly susceptible to these insults. Alveolarization continues through childhood and into adolescence, with the majority of alveoli forming postnatally

(18). Interference with this process through ETS-induced inflammation and oxidative stress may reduce final alveolar number and alter airway architecture, with permanent consequences for lung function trajectories (7,19). Schultz et al. identified infancy ETS exposure as an independent predictor of lung function growth between childhood and adolescence, suggesting that early-life exposures program later respiratory health (7). This developmental programming hypothesis is supported by animal studies demonstrating that perinatal nicotine exposure alters lung structure and function through effects on collagen deposition, elastin organization, and airway smooth muscle development (20).

**Specific Lung Function Parameters Affected**

A notable finding of this review is the differential impact of ETS exposure across lung function parameters, with small airway measures (FEF25-75, FEF25, FEF75) showing more consistent and substantial effects than larger airway measures (FEV1, FVC). He et al. reported that high ETS exposure (>5 cigarettes/day) was associated with reduced growth rates of FEF25-75 ($\beta = -0.104$, $p = 0.020$) and FEF25 ($\beta = -0.077$, $p = 0.027$), with clear monotonic exposure-response relationships, while effects on FEV1 and FVC were less robust (1). Bhargava et al. similarly found significantly lower FEF25-75% in adolescents exposed to paternal smoking (2), and Dai et al. reported substantial MEF25-75 reductions of 430 ml/s (95% CI: −798, −61) in perinatally exposed girls (5).

This pattern is biologically coherent, as small airways (those <2 mm in diameter) are the primary site of initial airway obstruction in smoking-related lung disease (21). Their greater surface area-to-volume ratio renders them more vulnerable to inhaled irritants, and they lack the cartilaginous support present in larger airways, making them more susceptible to collapse when inflamed or narrowed (22). Furthermore, standard spirometric measures such as FEV1 primarily reflect larger airway function and may remain within normal ranges despite significant small airways disease, a phenomenon termed the "quiet zone" of the lung (23). The finding that FEF25-75 and related measures are more sensitive indicators of ETS-related injury suggests that reliance on FEV1 and FVC alone may underestimate the true burden of ETS-induced lung damage in adolescents.

The FEV1/FVC ratio, a key indicator of airflow obstruction, also showed consistent deficits across multiple studies. Guerra et al. found a 2.8% lower pre-bronchodilator FEV1/FVC at age 26 among those with combined parental and active smoking exposure (95% CI: 0.9%–4.8%, p = 0.003) (11). Dai et al. reported a −0.038 reduction in FEV1/FVC in perinatally exposed girls (95% CI: −0.065, −0.010) (5). These reductions, while modest in absolute terms, are clinically significant at the population level, as even small downward shifts in the distribution of lung function increase the proportion of individuals falling below clinically relevant thresholds (24).

Studies using peak expiratory flow rate (PEFR) as the outcome measure similarly demonstrated negative associations. Soemarwoto et al. found significantly lower predicted PEFR in passive smokers (87.81) compared to controls (92.56, p = 0.04) (14). Sanghvi et al. demonstrated that PEFR improved significantly after 3 months of discontinuation of passive smoking exposure (12), providing quasi-experimental evidence for causality and suggesting at least partial reversibility of ETS effects. However, PEFR is more effort-dependent and variable than spirometric measures, and its use as a primary outcome may introduce measurement error (25).

**Dose-Response Relationships**

Evidence for dose-response relationships strengthens causal inference regarding ETS effects on lung function. He et al. provided the strongest formal testing, demonstrating significant p-values for trend across ETS exposure categories (non-exposed, 1-5 cigarettes/day, >5 cigarettes/day) for multiple respiratory symptoms and a monotonic exposure-response relationship for FEF25 and FEF25-75 growth rate deficits (1). This pattern, where increasing exposure levels are associated with progressively greater lung function decrements, satisfies a key criterion for causality in environmental epidemiology (26).

Guerra et al. showed that cumulative pack-years of parental smoking were associated with greater FEV1/FVC deficits, consistent with a dose-response pattern (11). Although formal trend testing was not reported, the monotonic relationship across exposure categories supports dose-dependent effects. Sanghvi et al. reported that frequency of smoking was associated with lower PEFR values, suggesting a dose-response gradient, though this was not formally tested (12). Milanzi et al. found consistent negative associations across all time windows of SHS exposure, with the magnitude

of effect increasing with the number of exposure sources, though formal dose-response testing was not conducted (4).

The absence of formal dose-response testing in many studies represents a significant limitation. Only four studies explicitly tested for or reported dose-response relationships (1,4,11,12), and among these, testing methods varied considerably. This methodological heterogeneity complicates efforts to identify threshold effects—levels of exposure below which no adverse effects occur—which are essential for establishing evidence-based standards for smoke-free environments. The available evidence suggests a linear or monotonic relationship without clear thresholds, implying that any level of ETS exposure may carry some risk (1,27).

**Effect Modification**

**Sex Differences:** One of the most striking findings was evidence for sex-specific susceptibility to ETS effects. Dai et al. found that perinatal smoke exposure was associated with significantly reduced lung function and increased asthma risk in girls but not boys (pre-bronchodilator FEV1: −272 ml/s in girls vs +26 ml/s in boys) (5). This differential effect persisted at ages 12 and 18 years and was observed across multiple lung function parameters. Several potential mechanisms may explain this finding. Girls have smaller airways relative to lung size compared with boys, a phenomenon termed dysanapsis (28). This structural difference may render their airways more susceptible to the effects of inhaled irritants. Hormonal factors may also play a role, as estrogen can modulate inflammatory responses and has been shown to interact with tobacco smoke components (29). Additionally, sex differences in detoxification enzyme expression and activity have been documented, potentially altering the metabolism of tobacco smoke constituents (30).

However, this finding was not universally replicated. Luttmann-Gibson et al. found no effect modification by sex in their analysis of air pollution effects, though ETS was not the primary exposure (19). Kostikas et al. did not observe sex differences in acute responses to ETS exposure, though their sample size was limited (n=18) and included only adults (15). Sanghvi et al. reported no sex differences in PEFR improvement following exposure cessation (12). The inconsistent findings may reflect differences in exposure assessment methods, outcome measures, study power, or true population differences. The Bhargava et al. study included only males (2), precluding sex comparison.

Given the limited replication of sex-specific effects, the Dai et al. findings should be interpreted cautiously, though they align with emerging evidence from adult COPD epidemiology suggesting differential female susceptibility to tobacco smoke (31).

**Genetic Polymorphisms:** Three studies examined gene-environment interactions, providing evidence that genetic variation modifies individual susceptibility to ETS-induced lung function decrements. Zhang et al. found that among children exposed to tobacco smoke, those with the Arg16 polymorphism in the β2-adrenoceptor gene had substantially lower FEV1 (2.19 vs 2.38 L) and FVC (2.43 vs 2.64 L) compared to Gly16 homozygotes (9). The β2-adrenoceptor is expressed on airway smooth muscle and inflammatory cells, and polymorphisms in this gene have been associated with altered receptor function, bronchodilator responsiveness, and asthma phenotypes (32). The Arg16 variant results in enhanced receptor downregulation following agonist exposure, which may impair airway smooth muscle relaxation and enhance susceptibility to irritant-induced bronchoconstriction (33).

Murdzoska et al. found that GSTP1 polymorphisms modulated the effects of tobacco smoke on lung function and airway responsiveness at ages 6, 12, and 18 years (10). Glutathione S-transferases are phase II detoxification enzymes that conjugate glutathione to electrophilic compounds, facilitating their excretion. GSTP1 is the predominant GST isoform expressed in the lung, and the Ile105Val polymorphism results in reduced enzyme activity (34). Individuals with the valine variant may have impaired capacity to detoxify tobacco smoke constituents, leading to greater oxidative stress and tissue damage. Interestingly, Murdzoska et al. found that protective effects were inconsistent across time points, suggesting age-dependent effects or potential confounding by other factors (10).

In contrast, Brehm et al. found no statistically significant gene-by-ETS interactions for SNPs in TNS1, ADAM19, and THSD4 after correction for multiple testing (20). These genes were selected based on genome-wide association studies for lung function in adults, and the null findings may reflect inadequate power for interaction testing, true absence of interaction, or the possibility that these genes operate through pathways not modified by ETS exposure. The discrepancy between positive and null findings underscores the need for adequately powered replication studies and

highlights the challenges of gene-environment interaction research, including multiple testing burdens, measurement error in environmental exposures, and population stratification (35).

**Timing of Exposure:** Consistent evidence emerged that the timing of ETS exposure critically influences effect magnitude. Studies measuring prenatal or perinatal exposure consistently reported the largest effect sizes. Dai et al. found a 272 ml/s reduction in FEV1 associated with perinatal exposure in girls (5), and Guerra et al. demonstrated that parental smoking at birth acted synergistically with later active smoking to produce a 2.8% FEV1/FVC deficit (11). Henderson et al. concluded that the strongest associations between smoke exposure and pulmonary function were with prenatal and early childhood exposure (6). Schultz et al. explicitly identified infancy ETS exposure as the only time window independently predictive of lung function growth between childhood and adolescence (7).

This pattern is consistent with the developmental origins of health and disease (DOHaD) hypothesis, wherein exposures during critical windows of development have lasting effects on organ structure and function (36). Lung development proceeds through distinct phases: embryonic, pseudoglandular, canalicular, saccular, and alveolar (37). The alveolar phase begins in utero and continues through early childhood, with approximately 85% of alveoli forming postnatally (38). Disruption of alveolarization through ETS-induced inflammation, oxidative stress, or direct toxicity may reduce final alveolar number and alter airway architecture, with permanent consequences for lung function trajectories (39). Furthermore, prenatal exposure may program epigenetic modifications that alter gene expression patterns and disease susceptibility throughout the life course (40).

In contrast, studies measuring current childhood ETS exposure tended to find smaller, though still significant, effects. Milanzi et al. found a −0.34% annual FEV1 growth reduction with childhood SHS exposure (4), and He et al. found modest beta coefficients for FEF parameters with current domestic exposure (1). This pattern suggests that while current exposure contributes to ongoing lung function deficits, the most profound and potentially irreversible effects occur during early development. Henderson et al. additionally noted that the effect of ETS on respiratory symptoms appeared to diminish with increasing age of the child (6), potentially reflecting reduced exposure as children spend more time outside the home or developmental changes in susceptibility.

**Synergistic Effects:** Guerra et al. demonstrated a significant synergistic interaction between parental smoking and subsequent active smoking on lung function decline (interaction p = 0.02 at age 26) (11). Neither parental smoking alone nor active smoking alone produced significant FEV1/FVC deficits, but the combination resulted in a 2.8% deficit. This finding has profound implications, suggesting that ETS exposure during development primes the lung for enhanced susceptibility to the effects of active smoking later in life. Potential mechanisms include ETS-induced alterations in airway structure, persistent inflammation, epigenetic modifications, or impaired detoxification capacity that amplify the effects of subsequent exposures (41). From a public health perspective, this synergy implies that reducing ETS exposure during childhood may have benefits extending beyond immediate respiratory health to modify the consequences of later smoking initiation.

Wang et al. found a significant interaction between diet quality and ETS exposure on wheezing (pint = 0.011), where a high-quality diet was protective only among adolescents with high ETS exposure (13). This finding suggests that nutritional factors may modify susceptibility to ETS effects, potentially through antioxidant mechanisms. Diets rich in fruits and vegetables provide antioxidants including vitamins C and E, carotenoids, and flavonoids that may counteract ETS-induced oxidative stress (42). The observation that diet quality was protective only in the high ETS group implies threshold effects, where antioxidant defenses become relevant only when oxidative burden exceeds a certain level. This interaction has implications for intervention strategies, suggesting that nutritional supplementation or dietary improvement may benefit ETS-exposed adolescents specifically.

Schultz et al. reported that associations between air pollution and lung function appeared stronger in subjects with asthma at age 16 (7), and Luttmann-Gibson et al. found greater short-term ozone effects in asthmatic children (19). These findings suggest that pre-existing airway inflammation or hyperresponsiveness may amplify responses to ETS and other environmental exposures, consistent with the concept of compromised hosts being more susceptible to environmental insults (43). From a clinical perspective, this implies that adolescents with asthma represent a particularly vulnerable subgroup for whom ETS avoidance should be strongly emphasized.

**Reversibility of Effects**

The question of whether ETS-induced lung function deficits are reversible has critical implications for clinical practice and public health messaging. Sanghvi et al. provided important evidence that PEFR improved significantly within 3 months of discontinuing passive smoking exposure (12). This improvement was observed across all age groups (5-15 years) and was sustained at 6-month follow-up, suggesting that at least some component of ETS-related impairment is reversible with exposure cessation. The quasi-experimental design, with each participant serving as their own control, strengthens causal inference regarding the effects of cessation.

Kostikas et al. demonstrated acute reversibility within 180 minutes after a single 1-hour exposure (15), indicating that immediate physiological responses to ETS (bronchoconstriction, airway acidification) are readily reversible. However, the relationship between these acute effects and chronic changes is complex. Repeated acute insults may lead to chronic inflammation, airway remodeling, and irreversible structural changes over time (44). The longitudinal cohort data indicating that early-life exposure tracks with reduced lung function into adolescence (4,7) and young adulthood (11) implies that a component of early damage may be permanent, particularly when exposure occurs during critical developmental windows.

The balance between reversible and irreversible components likely depends on exposure timing, duration, intensity, and individual susceptibility factors. This has important implications for clinical practice. While preventing exposure entirely remains the primary goal, reducing or eliminating exposure at any age may confer benefits. For adolescents already exposed, cessation may improve lung function trajectories and reduce risk of future respiratory disease (12). This message should be incorporated into clinical counseling and public health campaigns to motivate exposure reduction efforts.

**Implications for Research**

This systematic review identifies multiple priorities for future research. First, there is a need for studies with standardized exposure assessment methods incorporating both questionnaire data and objective biomarkers (cotinine, hair nicotine) to improve exposure classification and enable cross-study comparisons. Biomarkers provide quantitative, objective measures of exposure that are not subject to recall bias and can capture exposure from all sources (53). However, they reflect relatively

recent exposure and may not capture cumulative or historical exposure patterns. Combining questionnaire data (which can capture source, timing, and duration of exposure) with biomarkers (which provide objective confirmation) may optimize exposure characterization.

Second, longitudinal studies with repeated lung function measurements through adolescence and into adulthood are needed to characterize lung function trajectories and identify critical windows of susceptibility. Such studies should begin prenatally or in early infancy to capture exposures during the most vulnerable periods and should follow participants through the period of lung function plateau in early adulthood (54). Repeated measurements enable trajectory analysis, which may be more sensitive to exposure effects than single time point comparisons and can identify whether deficits reflect reduced growth, earlier decline, or both (55).

Third, adequately powered studies of gene-environment interactions are needed to identify genetic determinants of susceptibility. Such studies require large sample sizes, careful control for population stratification, correction for multiple testing, and replication in independent populations (56). Consortium approaches combining data from multiple cohorts may be necessary to achieve adequate power. Identified susceptibility genes could inform mechanistic understanding and potentially enable personalized prevention strategies.

Fourth, studies examining potential reversibility of ETS effects following exposure reduction or cessation are needed, particularly in adolescent populations. Intervention studies that provide smoking cessation support to household members and measure subsequent changes in adolescent lung function could provide stronger evidence for causality and quantify the benefits of exposure reduction (57). Such studies should include objective exposure monitoring to verify reduction and should follow participants sufficiently long to detect changes in lung function trajectories.

Fifth, research examining interactions between ETS and other environmental exposures (air pollution, allergens, indoor dampness) is needed, as these exposures often co-occur and may have synergistic effects (58). Understanding these interactions is essential for comprehensive risk assessment and for identifying the most effective intervention strategies.

Sixth, studies in diverse populations across different geographic regions and socioeconomic contexts are needed to assess generalizability of findings. Most studies in this review came from high-

income countries, with limited representation from low- and middle-income countries where ETS exposure rates may be higher and coexposures more prevalent (59). The Soemarwoto et al. study from Indonesia (14) and He et al. study from China (1) provide important contributions from non-Western settings, but more research in diverse populations is needed.

Seventh, investigation of potential threshold effects using rigorous dose-response modeling is needed to inform evidence-based standards for smoke-free environments. Identification of exposure levels below which no adverse effects occur would have profound implications for policy, though the available evidence suggests that any exposure may carry some risk (27). Advanced statistical methods such as restricted cubic splines or fractional polynomials may better characterize dose-response relationships than categorical analyses (60).

**Implications for Clinical Practice**

The findings of this review have several implications for clinical practice. Healthcare providers caring for adolescents should routinely assess ETS exposure through structured questioning, as exposure remains common and has documented effects on lung function. The US Preventive Services Task Force recommends that clinicians ask parents and caregivers about tobacco use and provide cessation interventions when indicated (61). Extending this to include assessment of adolescent exposure, regardless of their own smoking status, is essential.

When ETS exposure is identified, clinicians should provide clear, non-judgmental counseling about the risks and benefits of exposure reduction or elimination. The evidence for at least partial reversibility of effects should be communicated to motivate behavior change (12). For adolescents with respiratory symptoms or diagnosed asthma, the message should be particularly strong given evidence for enhanced susceptibility in this group (7,19).

Lung function monitoring should be considered for adolescents with significant ETS exposure, particularly those with respiratory symptoms. Spirometry can document current function and establish a baseline for tracking changes over time. When interpreting spirometry results, clinicians should be aware that small airway measures (FEF25-75) may be more sensitive indicators of ETS effects than FEV1 or FVC alone (1,5,11). However, the greater variability of these measures should be considered in clinical decision-making.

For adolescents who smoke themselves, the synergistic interaction between ETS exposure and active smoking should be emphasized (11). These adolescents are at particularly high risk for lung function deficits and should receive intensive smoking cessation support. The finding that ETS exposure during childhood may prime the lung for enhanced susceptibility to active smoking effects underscores the urgency of preventing smoking initiation in exposed youth.

Nutritional counseling may have a role in mitigating ETS effects, given evidence that high-quality diet modifies the association between ETS and respiratory symptoms (13). While dietary modification should not replace exposure reduction efforts, encouraging consumption of antioxidant-rich fruits and vegetables may provide some benefit for exposed adolescents.

**Implications for Public Health Policy**

The evidence synthesized in this review supports strengthened public health policies to protect adolescents from ETS exposure. Comprehensive smoke-free legislation covering all indoor public places and workplaces has been shown to reduce ETS exposure and improve respiratory health in multiple populations (62). However, such legislation does not protect adolescents from exposure in private homes and vehicles, which remain important sources of exposure (63). Public health campaigns should emphasize the importance of smoke-free homes and cars, targeting parents and caregivers with messages about the risks to adolescent lung health.

School-based interventions can raise awareness about ETS risks and provide skills for avoiding exposure. Given that many adolescents spend substantial time in schools, ensuring these environments are smoke-free is essential. Policies prohibiting smoking on school grounds should be strictly enforced and extended to cover school events and activities (64).

For vulnerable populations identified in this review—including girls, those with genetic susceptibility variants (when identified clinically), adolescents with asthma, and those from low-income households where exposure rates are higher—targeted interventions may be warranted. Home-based interventions providing smoking cessation support to household members, combined with air purification or ventilation improvements where cessation is not achievable, may reduce exposure for these high-risk groups (65).

The evidence for dose-response relationships without clear thresholds supports efforts to achieve complete elimination of ETS exposure rather than simply reduction. While any reduction confers benefit, the goal should be zero exposure, particularly for vulnerable populations (27). This message should be clearly communicated in public health campaigns.

Regulatory approaches to reduce the attractiveness and availability of tobacco products, including taxation, plain packaging, and restrictions on marketing, contribute to reducing smoking prevalence and consequently ETS exposure (66). These population-level interventions should be maintained and strengthened as part of comprehensive tobacco control strategies.

**Strengths of This Review**

This systematic review has several strengths. It focuses specifically on adolescents as defined by WHO criteria, enabling developmental stage-specific conclusions. It includes comprehensive data extraction across multiple domains (study characteristics, exposure assessment, lung function measures, primary associations, effect sizes, dose-response, effect modifiers, confounding control). It synthesizes evidence from diverse study designs, allowing triangulation of findings. It critically evaluates methodological quality and identifies sources of heterogeneity. It examines evidence for effect modification by multiple factors. It considers evidence for reversibility of effects, which has important clinical implications.

## CONCLUSION AND RECOMMENDATIONS

**Summary of Findings**

This comprehensive systematic review of 20 sources examining the relationship between environmental tobacco smoke exposure and lung function in adolescents yields several important conclusions. The evidence consistently supports a negative association between ETS exposure and lung function parameters in adolescents, with the predominant finding across 85% of studies demonstrating detrimental effects. This consistency across diverse study designs, populations, and geographic settings strengthens confidence in the association.

Small airway function, as measured by FEF25-75 and related parameters, emerges as the most consistently and substantially affected domain, with larger effects observed than for FEV1 or FVC.

This pattern has biological plausibility given the anatomy and physiology of small airways and suggests that standard spirometric measures may underestimate the true burden of ETS-related airway injury in adolescents.

Evidence for dose-response relationships, where formally tested, supports causal interpretation of the association. He et al. demonstrated monotonic exposure-response relationships for FEF25 and FEF25-75 growth rate deficits, and Guerra et al. showed greater deficits with increasing cumulative pack-years of parental smoking. The absence of clear threshold effects suggests that any level of ETS exposure may carry some risk.

Critical effect modifiers have been identified. The timing of exposure is paramount, with prenatal and early childhood exposure associated with the largest effect sizes, consistent with developmental vulnerability during critical windows of lung growth. Sex differences are suggested by one well-conducted study showing greater effects in girls, though replication is needed. Genetic polymorphisms in β2-adrenoceptor and GSTP1 genes modify individual susceptibility, providing mechanistic insights and identifying potentially vulnerable subgroups. Synergistic interactions between ETS and subsequent active smoking, and between ETS and diet quality, have important implications for prevention and intervention.

At least partial reversibility of ETS effects following exposure cessation is supported by one quasi-experimental study and the acute reversibility demonstrated in experimental research. However, the tracking of early-life exposure effects into adolescence and young adulthood in longitudinal cohorts suggests that some component of early damage may be permanent, underscoring the importance of primary prevention.

The quality of evidence varies, with prospective birth cohorts providing the strongest causal inference and cross-sectional studies offering more limited evidence. Methodological heterogeneity in exposure assessment, outcome measurement, and confounding control complicates cross-study comparisons and synthesis.

**Recommendations**

Based on these findings, the following recommendations are made:

**For Research:**

1. Future studies should employ standardized ETS exposure assessment combining questionnaire data with objective biomarkers
2. Longitudinal designs with repeated lung function measurements through adolescence are needed to characterize trajectories
3. Adequately powered gene-environment interaction studies should be conducted to identify genetic determinants of susceptibility
4. Research on reversibility of ETS effects following exposure reduction is needed
5. Studies in diverse populations across different geographic and socioeconomic contexts should be prioritized
6. Investigation of potential threshold effects using rigorous dose-response modeling is warranted
7. Examination of interactions between ETS and other environmental exposures should be pursued

**For Clinical Practice:**

1. Healthcare providers should routinely assess ETS exposure in adolescents through structured questioning
2. When exposure is identified, clear counseling about risks and benefits of reduction should be provided
3. Lung function monitoring, including small airway measures, should be considered for significantly exposed adolescents, particularly those with respiratory symptoms
4. For adolescents who smoke themselves, intensive cessation support should be provided, with emphasis on synergistic risks

5. Nutritional counseling regarding antioxidant-rich diets may have adjunctive benefit

**For Public Health Policy:**

1. Comprehensive smoke-free legislation should be maintained and strengthened
2. Public health campaigns should emphasize the importance of smoke-free homes and vehicles
3. School-based interventions should raise awareness and provide exposure avoidance skills
4. Targeted interventions for vulnerable populations (girls, asthmatics, low-income households) should be developed
5. The goal of complete exposure elimination should be communicated, consistent with dose-response evidence
6. Population-level tobacco control measures should be maintained and strengthened

**Concluding Remarks**

Environmental tobacco smoke exposure during adolescence represents a modifiable risk factor with documented effects on lung function that may have lifelong consequences for respiratory health. The evidence synthesized in this review demonstrates consistent negative associations, dose-response relationships, biological plausibility, and identification of susceptible subgroups, collectively supporting causal inference. While the magnitude of individual-level effects may be modest, the population-level impact is substantial given the high prevalence of ETS exposure among adolescents globally. Protecting adolescents from ETS exposure through comprehensive policies, clinical interventions, and public health programs should remain a priority to optimize lung health across the life course and reduce the burden of chronic respiratory disease in future generations.

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