

Reversible pulmonary function impairment in female patients with nickel sensitization: a cross-sectional observational study

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Abstract

Introduction: Nickel allergy is among the most common contact hypersensitivities worldwide. It affects women predominantly. This study examined whether female nickel-sensitized patients exhibit reversible changes in pulmonary function following a period of nickel avoidance.

Aim: To evaluate pulmonary functional parameters (PFPs) in female patients with nickel sensitization and assess changes after nickel avoidance.

Materials and methods: Twelve adult women with confirmed nickel hypersensitivity underwent spirometry before and after a 3-month nickel avoidance program. Measured parameters included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), peak expiratory flow (PEF), and the FEV₁/FVC ratio. Paired-sample tests and effect sizes were calculated.

Results: All indices changed significantly after avoidance. FVC increased from 2.7±0.7 L to 3.4±0.5 L [t(11)=-5.50, p<0.001, d_z=1.59]; FEV₁ from 2.4±0.6 L to 2.9±0.4 L [t(11)=-4.68, p=0.001, d_z=1.35]; PEF from 3.9±1.3 L/s to 6.1±0.5 L/s [t(11)=-6.81, p<0.001, d_z=1.97]; and the FEV₁/FVC ratio from 82.9±2.9% to 89.6±7.5% [t(11)=4.39, p=0.001, d_z=1.27].

Conclusion: In women with nickel allergy, pulmonary function improves significantly after nickel avoidance. Pulmonary assessment and avoidance counseling should be integrated into the management of female nickel-sensitized patients with respiratory symptoms.

Keywords

Nickel allergy, pulmonary function, airway inflammation, respiratory health, female reactions

Introduction

Nickel (Ni) is one of the most widespread transition metals in the environment and a leading cause of allergic contact dermatitis (ACD) worldwide.^[1] Beyond its dermatologic implications, nickel exposure may elicit systemic immune reactions that extend to the respiratory tract, particularly in sensitized individuals. Nickel compounds are used

extensively in alloys, jewelry, cosmetics, and industrial products; therefore, both cutaneous and inhalational exposures are common.^[2] Although the skin is the primary site of sensitization, increasing evidence indicates that nickel may also affect mucosal immunity and pulmonary physiology through inflammatory and oxidative mechanisms.^[3] Nickel allergy affects approximately 10%–20% of adults, with a marked predominance in women, attrib-

ed to frequent contact with nickel-containing jewelry and personal items.^[4] The immunopathogenesis of nickel hypersensitivity involves a type IV delayed hypersensitivity response mediated by CD4⁺ and CD8⁺ T lymphocytes. Upon re-exposure, nickel ions penetrate the epithelial barrier and bind to endogenous proteins, forming hapten-protein complexes that activate antigen-presenting cells.^[5] Subsequent cytokine release, such as interferon- γ (IFN- γ), tumor necrosis factor- α (TNF- α), and interleukin-17 (IL-17) sustains a proinflammatory environment.^[6]

Although well characterized in the skin, these mechanisms may also be activated within the respiratory mucosa following inhalational exposure to nickel containing particles (Fig. 1).

Epidemiological studies show that 12%–18% of nickel-sensitized individuals exhibit respiratory symptoms such as episodic wheeze or cough, increasing the clinical relevance of pulmonary evaluation.^[7]

In the respiratory system, nickel compounds interact directly with epithelial cells lining the bronchi and alveoli.^[8] Experimental data demonstrate that nickel nanoparticles can induce epithelial injury, tight-junction disruption, and the release of proinflammatory cytokines including IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF).^[9] These mediators promote recruitment of neutrophils and eosinophils, contributing to airway inflammation and mucus hypersecretion.^[10] In sensitized individuals, nickel may amplify Th2-mediated immune re-

sponses, leading to enhanced expression of IL-4, IL-5, and IL-13, cytokines known to promote airway hyperreactivity and remodeling.^[11]

This inflammatory milieu mirrors aspects of allergic asthma, suggesting that nickel hypersensitivity may precipitate reversible functional impairment even in the absence of chronic respiratory disease.^[12] Nickel-induced oxidative stress represents another critical pathway linking exposure to pulmonary dysfunction. Reactive oxygen species (ROS) generated by nickel can activate redox-sensitive transcription factors such as nuclear factor κ B (NF- κ B) and activator protein-1 (AP-1), leading to the upregulation of inflammatory genes.^[13] Mitochondrial dysfunction and lipid peroxidation further perpetuate epithelial injury. These oxidative mechanisms also modulate the expression of heme oxygenase-1 and superoxide dismutase, indicating a cellular effort to counteract oxidative injury.^[14] Over time, chronic oxidative imbalance may impair mucociliary clearance and increase airway resistance, contributing to reductions in forced expiratory volume (FEV₁) and peak expiratory flow (PEF). Such effects are consistent with spirometry alterations observed in occupational settings involving nickel exposure.^[15] The downstream consequence of persistent airway inflammation and oxidative stress is hyperreactivity of bronchial smooth muscle.^[16] Nickel exposure increases intracellular calcium levels and sensitizes β -adrenergic pathways, leading to bronchoconstriction.^[17] In animal models, nickel chloride inhalation provokes airway hyper-

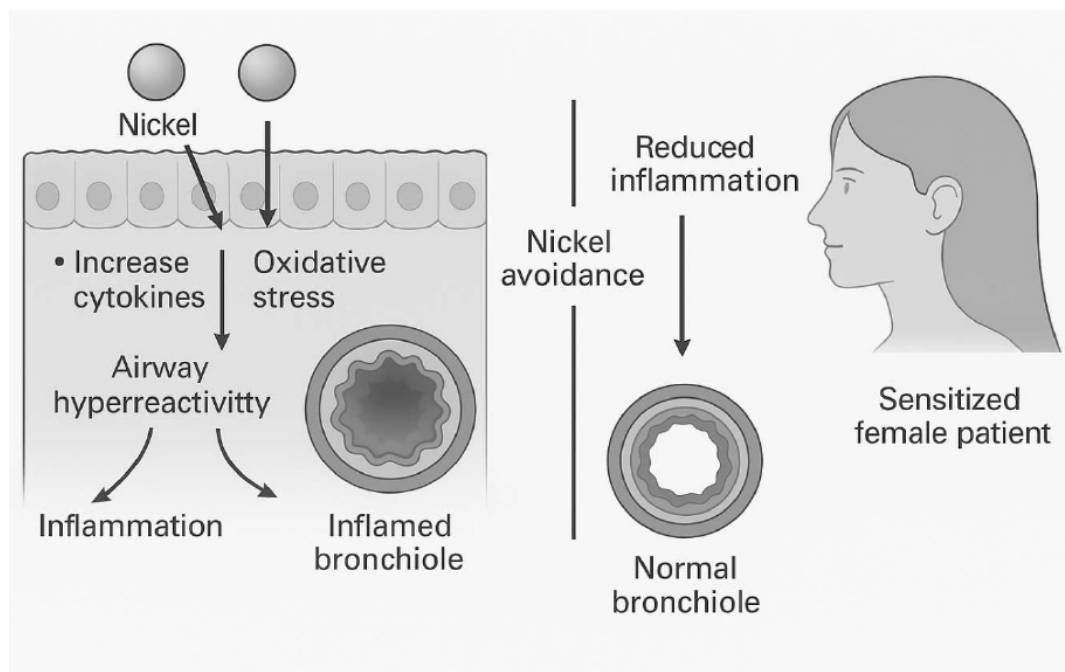


Figure 1. Pathophysiological mechanism of nickel-induced airway inflammation and reversibility process after nickel avoidance. Nickel exposure through direct skin contact or inhalation leads to epithelial penetration, oxidative stress, and cytokine release (IL-6, IL-8, TNF- α), triggering systemic inflammation and airway hyperreactivity. The inflamed bronchiole illustrates narrowed airways and epithelial damage associated with sensitization. Following strict nickel avoidance, inflammation and oxidative stress subside, epithelial integrity is restored, and airway function normalizes. This mechanism highlights how dermatologic sensitization to nickel can extend to the respiratory tract and demonstrates the reversible nature of these changes in sensitized female patients.

responsiveness accompanied by elevated eosinophilic infiltration and peribronchial inflammation.^[18] Importantly, these changes are not necessarily irreversible. Studies show that nickel withdrawal or avoidance can reduce cytokine production, restore epithelial integrity, and normalize airway mechanics within weeks.^[19]

This reversibility underscores the importance of early recognition and management of nickel induced respiratory manifestations.^[20] Females represent the majority of nickel-sensitized individuals and often present with a combination of dermatological and mild respiratory symptoms such as cough, dyspnea, or throat irritation after exposure.^[21] The interplay between cutaneous and airway sensitization suggests a shared immunologic pathway.^[22] Moreover, hormonal influences on immune modulation may further enhance susceptibility to nickel-induced airway effects in women.^[23] Given the global rise in environmental allergens, understanding how nickel sensitization impacts pulmonary function in this population has both clinical and preventive significance.^[24]

Despite increasing recognition of systemic manifestations of metal hypersensitivity, few studies have examined pulmonary function in non-occupationally exposed individuals with confirmed nickel allergy.^[25] The potential reversibility of nickel-associated airway impairment following allergen avoidance remains insufficiently explored.^[25] In this context, the present study evaluated the pulmonary functional parameters in female patients with confirmed nickel sensitization before and after a structured nickel avoidance period.

Aim

By focusing on reversible changes in spirometry indices such as FVC, FEV₁, PEF, and FEV₁/FVC ratio, this study provides novel insight into the functional respiratory consequences of nickel allergy and the potential benefits of avoidance strategies.

Materials and methods

Study design and participants

This investigation was designed as a single-center, cross-sectional observational study conducted at the Institute of Pathophysiology and the Respiratory Laboratory Unit, with patients coming from Clinics of Dermatology and Allergology, University Clinical Center of Kosovo (UCCK), Prishtina. The study was approved by the Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment.

A total of 17 adult female patients aged 20–60 years with suspected nickel hypersensitivity were initially recruited

from the outpatient clinic between January 2022 and May 2025. Diagnosis of nickel sensitization was confirmed by patch testing with nickel sulfate (5% in petrolatum, European baseline series, ICDRG criteria).^[26]

Of the 17 participants, five were excluded for the following reasons: two did not attend the second follow-up spirometry visit, one developed an acute respiratory infection during the study period, one reported inconsistent adherence to the nickel-avoidance protocol, and one was excluded due to incomplete spirometry data. Consequently, the final analysis included 12 confirmed female patients with complete baseline and follow-up assessments. None of the participants had chronic respiratory disease, recent respiratory infections, occupational metal exposure, or regular use of corticosteroids or bronchodilators.

Nickel avoidance protocol

After the baseline evaluation, each participant received standardized written and verbal guidance for nickel avoidance. The protocol included the elimination of direct skin contact with nickel-containing jewelry, fasteners, eyeglass frames, and mobile phone cases; avoidance of foods with high nickel content (e.g., nuts, cocoa, chocolate, legumes, oatmeal, soy, and canned foods); and the use of nickel-free cooking utensils. Compliance was monitored monthly via structured telephone interviews.

The second spirometry assessment was performed three months after initiation of nickel avoidance.

Adherence was assessed by structured interviews only; no biochemical validation (e.g., urinary nickel levels) was available, representing a methodological limitation.

Pulmonary function testing

Pulmonary function was measured using a Spirolab III desktop spirometer (Medical International Research, Italy) in accordance with the 2019 ATS/ERS standards. Each subject performed at least three acceptable maneuvers, and the best effort was recorded. The parameters measured included:

- FVC (forced vital capacity, L),
- FEV₁ (forced expiratory volume in 1 s, L),
- FEV₁/FVC ratio (%), and
- PEF (peak expiratory flow, L/s).

Predicted reference values were derived according to Crapo & Bass/Knudson equations adjusted for age, height, and gender. Calibration of the spirometer was verified before each session.

Data analysis

All statistical analyses were performed using SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was applied to assess normality. For normally distributed variables, paired-samples t-tests were

used to compare pulmonary parameters before and after the three-month nickel-avoidance period. When normality assumptions were not met, the Wilcoxon signed-rank test was applied as a non-parametric alternative.

Beyond statistical significance ($p < 0.05$), effect sizes were calculated using Cohen's d_z , which quantifies the magnitude of within-subject change for paired-sample designs. The effect size was obtained by dividing the mean difference between pre- and post-measurements by the standard deviation of the difference scores ($d_z = \Delta_{\text{mean}} / \text{SD}_{\Delta}$). According to Cohen's (1988) conventions, $d_z \approx 0.2$ indicates a small effect, ≈ 0.5 a medium effect, and ≥ 0.8 a large effect.

All tests were two-tailed with a significance level of $\alpha = 0.05$. Descriptive and inferential results were summarized in tables, and graphical visualizations (Fig. 2(A-D)) were prepared using SPSS and verified in Microsoft Excel 365 for consistency.

Results

Study population

Out of 17 initially enrolled female participants with clin-

ically suspected nickel hypersensitivity, 12 patients (mean age, 44.9 ± 3.0 years) completed both baseline and follow-up evaluations and were included in the final analysis. The remaining five participants were excluded due to missing follow-up visits ($n=2$), acute respiratory infection ($n=1$), incomplete spirometry data ($n=1$), or non-compliance with nickel-avoidance instructions ($n=1$).

All 12 included patients had positive patch tests according to ICDRG criteria. None had a history of chronic pulmonary disease, recent smoking cessation within < 3 months, or medication use influencing respiratory function.

The mean body mass index (BMI) was 24.9 ± 3.8 kg/m² (range = 18.3–31.2 kg/m²). Three patients were current smokers, two ex-smokers, and seven were non-smokers.

Pulmonary function before and after nickel avoidance

At baseline, mild reductions in pulmonary function parameters were observed in most patients compared with predicted reference values (Crapo & Bass/Knudson equations).

Baseline spirometry values (e.g., FEV₁ 78%–84% predicted) were borderline low but not clinically abnormal.

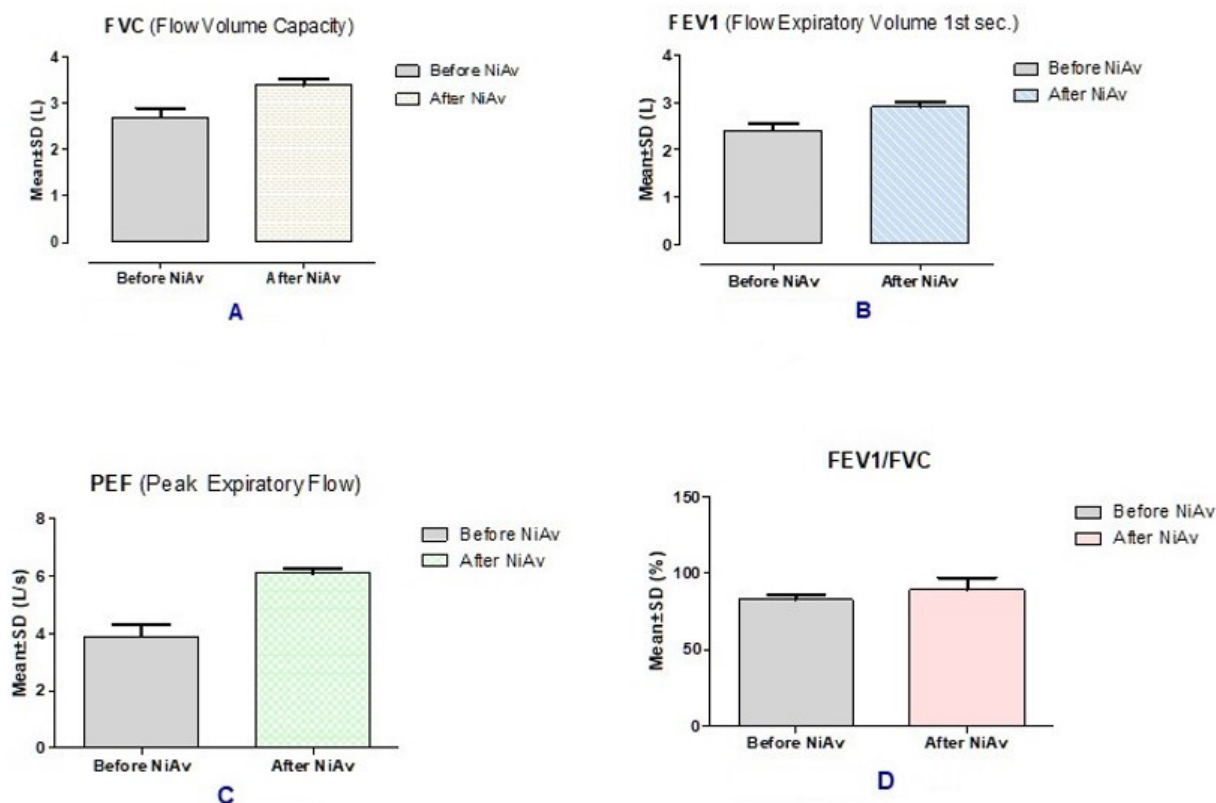


Figure 2. Mean \pm SD values of pulmonary function parameters before and after a 3-month nickel-avoidance program in 12 female patients with confirmed nickel hypersensitivity. (A) Forced Vital Capacity (FVC) increased significantly ($p < 0.001$, $d_z = 1.59$); (B) Forced Expiratory Volume in 1 s (FEV₁) improved markedly ($p = 0.001$, $d_z = 1.35$); (C) Peak Expiratory Flow (PEF) demonstrated the largest relative gain ($p < 0.001$, $d_z = 1.97$); (D) FEV₁/FVC ratio increased ($p = 0.001$, $d_z = 1.27$), indicating partial reversibility of airway obstruction. All effect sizes represent large within-subject improvements according to Cohen's conventions.

After three months of strict nickel avoidance, all measured indices improved substantially (Table 1 and Fig. 2(A-D)).

- Forced vital capacity (FVC) increased from 2.7 ± 0.7 L to 3.4 ± 0.5 L, representing a mean gain of $+0.70$ L, [$t(11) = -5.50$, $p < 0.001$, $d_z = 1.59$] (Fig. 2A).
- Forced expiratory volume in 1 s (FEV₁) rose from 2.4 ± 0.6 L to 2.9 ± 0.4 L, mean change $+0.50$ L, [$t(11) = -4.68$, $p = 0.001$, $d_z = 1.35$] (Fig. 2B).
- Peak expiratory flow (PEF) improved markedly from 3.9 ± 1.3 L/s to 6.1 ± 0.5 L/s, [$t(11) = -6.81$, $p < 0.001$, $d_z = 1.97$] (Fig. 2C).
- The FEV₁/FVC ratio increased from $82.9 \pm 2.9\%$ to $89.6 \pm 7.5\%$, indicating partial reversibility of airway obstruction [$t(11) = 4.39$, $p = 0.001$, $d_z = 1.27$] (Fig. 2D).

According to Cohen's benchmarks, all observed effect sizes were large ($d_z > 0.8$), reflecting not only statistically significant but also clinically meaningful improvements in pulmonary function following nickel avoidance.

Additional spirometry indices

Secondary indices, including mid-expiratory flow rates (FEF_{25-75%}) and FEV₆, also demonstrated consistent improvement. Mean FEF_{25-75%} increased from 3.35 ± 0.54 L/s to 4.62 ± 0.70 L/s ($p < 0.001$), while FEV₆ rose from 2.56 ± 0.45 L to 3.18 ± 0.38 L ($p < 0.01^*$).

These findings suggest a reduction in small-airway dysfunction following nickel avoidance.

Clinical correlations

Patients who initially reported both dermatologic and respiratory symptoms ($n=8$) experienced the most pronounced improvements in spirometry parameters, particularly in PEF and FEV₁/FVC ratio ($p < 0.01^*$), whereas those with isolated cutaneous manifestations ($n=4$) exhibited more modest but still significant gains. No adverse reactions or respiratory events occurred during the follow-up period.

Table 1. Pre-post comparison of pulmonary function ($n=12$, female patients)

Parameter	Pre Mean \pm SD	Post Mean \pm SD	Δ (Post-Pre)	t(11)	p-value	95% CI of Δ	Cohen's d_z
FVC (L)	2.7 ± 0.7	3.4 ± 0.5	+0.70	-5.50	<0.001	[+0.41, +0.99]	1.59
FEV1 (L)	2.4 ± 0.6	2.9 ± 0.4	+0.50	-4.68	0.001	[+0.26, +0.74]	1.35
PEF (L/s)	3.9 ± 1.3	6.1 ± 0.5	+2.20	-6.81	<0.001	[+1.47, +2.93]	1.97
FEV1/FVC (%)	82.9 ± 2.9	89.6 ± 7.5	+6.70	4.39	0.001	[+3.30, +10.10]	1.27

Subgroup analyses

1. BMI-based comparison

- Patients with normal BMI (< 25 kg/m²; $n=7$) showed greater improvements in all spirometry parameters compared with those who were overweight (≥ 25 kg/m²; $n=5$).
- The mean increases in FEV₁ among normal-BMI patients was $+0.59$ L vs. $+0.33$ L in the overweight group [$t(10) = 2.63$, $p = 0.024$].
- The mean PEF gain was $+2.5$ L/s vs. $+1.6$ L/s, respectively ($p = 0.018$).
- These differences suggest that higher BMI may partially attenuate the functional recovery associated with allergen avoidance, possibly due to mechanical and inflammatory contributions to reduced lung volumes.

2. Smoking status

No statistically significant differences were observed between smokers ($n=3$) and non-smokers/ex-smokers ($n=9$) in the magnitude of improvement for FVC, FEV₁, or PEF ($p > 0.05$ for all comparisons). However, descriptive trends indicated slightly smaller relative increases among current smokers, consistent with previous findings that airway irritants may limit reversibility even in allergic conditions.

Summary findings

Table 1 presents descriptive statistics and paired comparisons for the main pulmonary function parameters. Fig. 2(A-D) graphically illustrates the pre- and post-avoidance changes in mean FVC, FEV₁, PEF, and FEV₁/FVC ratio, confirming consistent upward trends across the cohort.

The data collectively indicate that improvement was observed following a period of advised nickel avoidance in pulmonary function among nickel-sensitized female patients. The magnitude of the effect ($d_z = 1.27-1.97$) underscores the clinical relevance of respiratory screening and counseling in this population.

Discussion

This study provides novel evidence that nickel hypersensitivity in women may be associated with reversible pulmonary function impairment, with significant improvements in spirometric parameters following a structured three-month nickel-avoidance program. Although nickel allergy is well established as a major cause of contact dermatitis, its potential systemic and respiratory implications remain largely underexplored, particularly in non-occupational-

ly exposed individuals.^[28] The current findings therefore broaden the clinical understanding of nickel sensitization beyond dermatological manifestations, suggesting that the allergen may also exert functional effects on the respiratory system that are at least partially reversible upon avoidance.^[29]

The present cohort consisted exclusively of female patients, consistent with the known epidemiology of nickel hypersensitivity, which disproportionately affects women due to higher exposure to nickel-releasing jewelry and personal items. Nickel is a potent immunologic hapten capable of inducing type IV delayed hypersensitivity reactions, involving activation of T-lymphocytes, macrophages, and pro-inflammatory cytokine release (IL-1 β , TNF- α , IFN- γ).^[30] Repeated dermal exposure or systemic absorption of nickel may prime both skin and airway epithelial immune responses, promoting localized inflammation and oxidative stress that could transiently alter pulmonary function.^[31]

The observed improvements in FVC, FEV₁, PEF, and FEV₁/FVC ratio following nickel avoidance were not only statistically significant but also clinically meaningful, with large effect sizes ($d_z=1.27-1.97$). These magnitudes exceed those reported in studies of mild asthma or allergic rhinitis after short-term allergen reduction^[32], suggesting that nickel sensitization may contribute to measurable yet reversible airway dysfunction. Mechanistically, the inhalation or ingestion of trace nickel may act as a non-specific airway irritant, triggering epithelial activation, neutrophil recruitment, and oxidative injury.^[33] Experimental data show that nickel nanoparticles can increase airway resistance and induce bronchial inflammation in animal models^[34], while occupational studies have demonstrated diminished FEV₁ among nickel refinery workers^[35]. The current study extends this evidence to a non-industrial, female population with contact hypersensitivity rather than direct occupational exposure.

Subgroup analyses in this cohort revealed that women with normal BMI (<25 kg/m²) experienced significantly greater functional recovery compared to overweight subjects. This aligns with previous observations that obesity is associated with reduced lung compliance, increased airway closure, and systemic low-grade inflammation, all of which may blunt responsiveness to environmental or therapeutic interventions.^[36] Conversely, the absence of significant differences between smokers and non-smokers suggests that, within the small number of current smokers in this sample, tobacco exposure did not markedly influence the direction of nickel-related functional changes, although the sample size limits firm conclusions.

An additional finding of note is the improvement in mid-expiratory flow rates (FEF_{25-75%}), which are sensitive markers of small-airway function. This supports the hypothesis that nickel-induced inflammation may primarily affect distal airways. The normalization of these indices after nickel avoidance is consistent with a reduction in small-airway obstruction, as previously observed in aller-

gic asthma after exposure cessation.^[21] Collectively, these data reinforce the pathophysiological link between allergic sensitization and subclinical bronchial hyperreactivity.

While the exact mechanism through which nickel avoidance improves lung function remains yet unclear, several plausible pathways exist. Removal of cutaneous and dietary sources of nickel likely decreases systemic nickel absorption and circulating nickel ions, reducing systemic oxidative stress and cytokine release, while minimizing respiratory exposure—for example, from household dust or metal vapor—may attenuate airway irritation. Further, nickel avoidance may indirectly improve pulmonary performance through enhanced mucociliary clearance and reduced epithelial inflammation. Together, these processes could explain the observed reversibility in spirometric measures.

From a clinical standpoint, these results underscore the importance of multidisciplinary assessment of nickel-sensitized patients who report respiratory complaints. Dermatologists and allergologists should consider incorporating spirometric screening into routine evaluation, particularly for female patients with co-existing respiratory symptoms. Education on allergen avoidance, often emphasized for cutaneous disease management, may also have systemic benefits. Early identification and avoidance could prevent progression to chronic airway disease in susceptible individuals.

Despite its strengths, this study has several limitations. The sample size (n=12) was relatively small, reflecting the strict inclusion criteria and the observational design. Nevertheless, the within-subject analysis and large effect sizes mitigate some of the concerns regarding power. The absence of a non-sensitized control group limits causal inference, and confounding factors such as environmental pollution or unrecognized atopy could not be fully excluded. Spirometric testing, while dependable, provides only functional data; future studies incorporating biomarkers of oxidative stress and airway inflammation (e.g., fractional exhaled nitric oxide, eosinophilic cationic protein) would strengthen mechanistic interpretation. Longitudinal studies with larger samples and both sexes are warranted to assess persistence and generalizability of the observed improvements.

Finally, although the nickel avoidance protocol was standardized and monitored, adherence relied partially on self-reporting, which may introduce bias. Objective measures such as nickel levels in urine or serum could enhance future methodological rigor. Nonetheless, the consistent direction and magnitude of functional improvement across all participants suggest genuine physiological recovery rather than measurement variability.

Conclusion

This study demonstrates that nickel sensitization in women may be associated with reversible impairment of pulmo-

nary function, independent of occupational exposure. A structured three-month program of nickel avoidance led to significant and clinically relevant improvements in FVC, FEV₁, PEF, and FEV₁/FVC ratio. These findings highlight the systemic implications of metal allergies and support the integration of pulmonary function testing into the clinical management of nickel-sensitized patients, particularly those with concomitant respiratory complaints.

The results advocate for a more holistic approach to nickel allergy that extends beyond dermatologic care to include respiratory evaluation and lifestyle counseling. Incorporating allergen-avoidance strategies may improve both skin and airway outcomes, enhancing overall quality of life.

Future research should explore immunologic and inflammatory biomarkers, involve larger cohorts with control groups, and evaluate long-term outcomes following sustained avoidance. A broader understanding of the respiratory impact of metal sensitization may inform both preventive strategies and multidisciplinary management in allergy and dermatology practice.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of the Faculty of Medicine and the Institute of Pathophysiology (Approval No. 111062;UCCCK-2022-41/FM=KMC-2025/5).

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that certain experiments on humans or human tissues were performed for the present study.

The authors declared that written informed consent was obtained from all participants before enrollment in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

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Conflict of Interest

The author declares no conflict of interest.

Data availability

All data used are referenced or included in the article.

Use of AI

The authors used ChatGPT to modify and polish the Cover Letter in order to comply with the Folia Medica journal's requirements during the preparation of this work.

Author contributions

BN and SD: conceptualization, study design, drafting the manuscript, critical review of the manuscript; SD and ShD: statistical analysis, interpretation of data, data collection; BN: literature review, data verification, manuscript editing. All authors have read and agreed to the published version of the manuscript.

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References

- Ahlström MG, Thyssen JP, Wennervaldt M, et al. Nickel allergy and allergic contact dermatitis: A clinical review of immunology, epidemiology, exposure, and treatment. *Contact Dermatitis* 2019; 81(4):227–41. doi: 10.1111/cod.13327
- Genchi G, Carocci A, Lauria G, et al. Nickel: human health and environmental toxicology. *Int J Environ Res Public Health* 2020; 17(3). Available from: <https://www.mdpi.com/1660-4601/17/3/679>
- Roach KA, Stefaniak AB, Roberts JR. Metal nanomaterials: Immune effects and implications of physicochemical properties on sensitization, elicitation, and exacerbation of allergic disease. *J Immunotoxicol* 2019; 16(1):87–124. Available from: <https://www.tandfonline.com/doi/pdf/10.1080/1547691X.2019.1605553>
- Tramontana M, Bianchi L, Hansel K, et al. Nickel allergy: epidemiology, pathomechanism, clinical patterns, treatment and prevention programs. *Endocr Metab Immune Disord Drug Targets* 2020; 20(7):992–1002.
- Kobayashi K, Kaneda K, Kasama T. Immunopathogenesis of delayed-type hypersensitivity. *Microsc Res Tech* 2001; 53(4):241–5.
- Belpaire A, Van Geel N, Speeckaert R. From IL-17 to IFN- γ in inflammatory skin disorders: Is transdifferentiation a potential treatment target? *Front Immunol* 2022; 13:932265. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9367984/>
- Roach K, Roberts J. A comprehensive summary of disease variants implicated in metal allergy. *J Toxicol Environ Health B Crit Rev* 2022; 25(6):279–341. Available from: <https://www.tandfonline.com/doi/abs/10.1080/10937404.2022.2104981>
- Lee HW, Jose CC, Cuddapah S. Epithelial-mesenchymal transi-

- tion: Insights into nickel-induced lung diseases. *Semin Cancer Biol* 2021; 76:99. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8627926/>.
9. Capasso L, Camatini M, Gualtieri M. Nickel oxide nanoparticles induce inflammation and genotoxic effect in lung epithelial cells. *Toxicol Lett* 2014; 226(1):28–34. Available from: <https://pubmed.ncbi.nlm.nih.gov/24503009/>.
 10. Ray A, Kolls JK. Neutrophilic Inflammation in asthma and association with disease severity. *Trends Immunol [Internet]* 2017; 38(12):942. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5711587/>.
 11. Glista-Baker EE, Taylor AJ, Sayers BC, et al. Nickel nanoparticles cause exaggerated lung and airway remodeling in mice lacking the T-box transcription factor, TBX21 (T-bet). *Part Fibre Toxicol* 2014; 11(1):7. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3931667/>.
 12. Kolberg L, Forster F, Gerlich J, et al. Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study. *ERJ Open Res* 2020; 6(1):00178–2019. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6995837/>.
 13. Freitas M, Gomes A, Porto G, et al. Nickel induces oxidative burst, NF- κ B activation and interleukin-8 production in human neutrophils. *J Biol Inorg Chem* 2010; 15(8):1275–83. Available from: <https://pubmed.ncbi.nlm.nih.gov/20632048/>.
 14. Bansal S, Biswas G, Avadhani NG. Mitochondria-targeted heme oxygenase-1 induces oxidative stress and mitochondrial dysfunction in macrophages, kidney fibroblasts and in chronic alcohol hepatotoxicity. *Redox Biol* 2013; 2(1):273. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3909819/>.
 15. Csonka LL, Tikkakoski A, Vuotari L, et al. Relation of changes in peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV1) during bronchoconstriction. *Clin Physiol Funct Imaging* 2024; 44(6):447–53. Available from: <https://pubmed.ncbi.nlm.nih.gov/38923340/>.
 16. Kume H, Yamada R, Sato Y, et al. Airway smooth muscle regulated by oxidative stress in COPD. *Antioxidants* 2023; 12(1):142. Available from: <https://www.mdpi.com/2076-3921/12/1/142>
 17. Cortijo J, Milara J, Mata M, et al. Nickel induces intracellular calcium mobilization and pathophysiological responses in human cultured airway epithelial cells. *Chem Biol Interact* 2010; 183(1):25–33. Available from: <https://pubmed.ncbi.nlm.nih.gov/19781536/>.
 18. Lapa E Silva JR, Ruffié C, Lefort J, et al. Role of eosinophilic airway inflammation in models of asthma. *Mem Inst Oswaldo Cruz* 1997; 92 (Suppl 2):223–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/9698939/>.
 19. Zhang X, Bradford B, Baweja S, et al. Nickel-induced transcriptional memory in lung epithelial cells promotes interferon signaling upon nicotine exposure. *Toxicol Appl Pharmacol* 2023; 481:116753. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11065478/>.
 20. Shekhar C, Khosya R, Thakur K, et al. A systematic review of pesticide exposure, associated risks, and long-term human health impacts. *Toxicol Rep* 2024; 13:101840. Available from: <https://www.sciencedirect.com/science/article/pii/S2214750024002233>
 21. Brera S, Nicolini A. Respiratory manifestations due to nickel. *Acta Otorhinolaryngologica Italica* 2005; 25(2):113. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2639879/>.
 22. Weinstock J, Chen XX, Nino G, et al. The interplay between airway epithelium and the immune system – a primer for the respiratory clinician. *Paediatr Respir Rev* 2021; 38:2. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC8178232/>.
 23. Yang J, Ma Z. Research progress on the effects of nickel on hormone secretion in the endocrine axis and on target organs. *Ecotoxicol Environ Saf* 2021; 213:112034. Available from: <https://www.sciencedirect.com/science/article/pii/S0147651321001457>
 24. Kolberg L, Forster F, Gerlich J, et al. Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study. *ERJ Open Res* 2020; 6(1):00178–2019. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6995837/>.
 25. Jomova K, Alomar SY, Nepovimova E, et al. Heavy metals: toxicity and human health effects. *Arch Toxicol* 2024; 99(1):153–209. Available from: <https://link.springer.com/article/10.1007/s00204-024-03903-2>
 26. Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing - Recommendations on best practice. *Contact Dermatitis* 2015; 73(4):195–221. doi: 10.1111/cod.12432
 27. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J* 2022; 60(1). Available from: <https://publications.ersnet.org/content/erj/60/1/2101499>
 28. Systemic Nickel Allergy Syndrome: An update | Request PDF [Internet]. [cited 2025 Nov 7]. Available from: https://www.researchgate.net/publication/287919941_Systemic_Nickel_Allergy_Syndrome_An_update
 29. Brera S, Nicolini A. Respiratory manifestations due to nickel. *Acta Otorhinolaryngologica Italica* 2005; 25(2):113. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2639879/>.
 30. Guo H, Liu H, Jian Z, et al. Nickel induces inflammatory activation via NF- κ B, MAPKs, IRF3 and NLRP3 inflammasome signaling pathways in macrophages. *Aging (Albany NY)* 2019; 11(23):11659. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6932914/>.
 31. Anderson SE, Meade BJ. Potential health effects associated with dermal exposure to occupational chemicals. *Environ Health Insights* 2014; 8(Suppl 1):51. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4270264/>.
 32. Farraia M, Paciência I, Castro Mendes F, et al. Allergen immunotherapy for asthma prevention: A systematic review and meta-analysis of randomized and non-randomized controlled studies. *Allergy: Eur J Allergy Clin Immunol* 2022; 77(6):1719–35. doi: 10.1111/all.15295
 33. Forti E, Salovaara S, Cetin Y, et al. In vitro evaluation of the toxicity induced by nickel soluble and particulate forms in human airway epithelial cells. *Toxicol Vitro* 2011; 25(2):454–61.
 34. Mo Y, Jiang M, Zhang Y, et al. Comparative mouse lung injury by nickel nanoparticles with differential surface modification. *J Nanobiotechnol* 2019; 17:1–18. Available from: <https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-018-0436-0>
 35. Syurin S, Vinnikov D. Occupational disease predictors in the nickel pyrometallurgical production: a prospective cohort observation. *J Occup Med Toxicol* 2022; 17(1):21. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9636620/>.
 36. Dixon AE, Peters U. The effect of obesity on lung function. *Expert Rev Respir Med* 2018; 12(9):755. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC6311385/>.