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Unveiling the Hidden Impact: Nicotine Metabolites on Health of Rural Women Beedi Rollers of Reproductive Age in Telangana Using Cutting-edge LC-MS Analysis

Authors
Penagaluru Pardhanandana Reddy[1,2], Baluka Vanitha[1], Busarapu Manideep[1], Shehnaz Sultana[1], Lakkampelly Madhuri[1], Ch. Prashanth[1]
[1]Bhagwan Mahavir Medical Research Centre, A.C. Guards, Hyderabad, Telangana, India
[2]MAA Research Foundation, Jubilee Hills, Hyderabad, Telangana, India
Corresponding Author
Prof. Penagaluru Pardhanandana Reddy
Research Director, Bhagwan Mahavir Hospital and Research Centre, AC Guards, Hyderabad, Telangana, India

Abstract

Background: *Beedi rolling is a prevalent small-scale industry in rural Telangana, providing employment for lakhs of women. Unlike previous studies relying on epidemiological methods, we employ a comprehensive approach, integrating demographic data analysis and quantification of nicotine metabolites through Liquid Chromatography Coupled with Mass Spectrometry (LCMS).*

Methods: *A cohort of 320 women employed as beedi rollers and 280 women with no occupational exposure to chemicals were included in the study. Participants, aged 15 to 50 years, were selected from various villages of Jagityal and Nizamabad Districts of Telangana. The research centered on diverse health issues, encompassing hematological parameters and outcomes related to reproduction. The quantification of nicotine metabolites and other toxic components in beedi rollers was conducted using LCMS.*

Results: *Demographic data analysis revealed significant distinctions in literacy rates and income between women engaged in beedi rolling and those not involved in the occupation. The hematological investigations disclosed, statistically significant decline in all haematological parameters among beedi rollers. The results also indicated an elevated incidence of tuberculosis, asthma and shoulder pain among individuals involved in beedi rolling. The findings also indicated elevated rates of infertility, miscarriage, and stillbirths in women beedi rollers. Statistical analysis confirmed a statistically significant increase in nicotine metabolites among beedi rollers.*

Conclusion: *The research highlights the influence of nicotine metabolites on overall health of women engaged in beedi rolling. There is a necessity to raise awareness among these women regarding the occupational risks they encounter.*

Introduction

Beedi rolling a prevalent small-scale industry in rural Telangana, serves as a source of employment for lakhs of rural women. Despite the labour-intensive nature of the work and relatively low wages, women in rural areas continue in this occupation due to the absence of alternative livelihood options. A distinct group of women in the beedi rolling industry, particularly in developing countries like India, faces occupational exposure to tobacco through both transdermal absorption and inhalation. Smoking during pregnancy is well-known for its adverse effects. However, there is a gap in research regarding the effects of transdermal absorption, as observed in women involved in beedi rolling. Until now, investigations into the health implications of beedi making have predominantly relied on epidemiological methods. Comprehensive studies specifically exploring the levels of nicotine and their effects on the health of women involved in beedi rolling are not adequately documented. In the rural areas of Telangana State, lakhs of women are involved in the practice of beedi rolling. Throughout their engagement in this occupation, these women face potential exposure to tobacco through skin contact, inhalation, or ingestion of food and water contaminated with tobacco dust. Therefore, it is crucial to comprehend their health issues and reproductive health. This understanding is essential for implementing preventive measures and welfare programs aimed at promoting their well-being. Nicotine, a naturally occurring botanical insecticide found in tobacco leaves, serves as the principal tobacco alkaloid, constituting approximately 1.5% by weight in commercially used cigarette tobacco and making up to about 95% of the total alkaloid content. The present study aims to investigate the health issues, and reproductive health of women involved in beedi rolling by estimating the nicotine metabolites in the rural areas of Telangana state from South India. Components of tobacco, including specific nitrosamines (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, N'-Nitrosonornicotine), Cotinine, Nornicotine, and Anabasine, will be quantified in the serum of individuals engaged in beedi rolling (BR) and those not involved in beedi rolling (NBR).

Materials and Methods

Study Subjects

The study involved a cohort of 320 women employed as beedi rollers and 280 women with no occupational exposure to chemicals for comparison. The study encompassed individuals aged between 15 and 50 years. Following the acquisition of informed consent from each participant, a standard questionnaire was utilized to collect information on various aspects, including age, gender, marital status, living conditions, habits, work duration, socio-economic status, daily working hours, tobacco usage, and both present and past health history. The study was conducted among women employed as beedi rollers in various villages, namely Ibrahimpatnam, Varshakonda, Sattakkapally, Mularampur, Vellulla, Bandalingapur, Chinthalpet, Yousufnagar, Korutla, Athmakur, Aarapet, Athmanagar, Godhur, Kanapur, Jaggasagar, Kathlapur, Metpally, Mogilpet, Thimmapur, and Vemulakurthi in the Jagityal District, as well as Kammarpally and Bhemghal in the Nizamabad District of Telangana State, India. Exclusions from the study involved individuals who consumed pan, gutka, or tobacco, and those with chronic diseases. As a comparison group, women residing in the same areas with similar socio-economic status, but without exposure to any chemical, including tobacco dust, were selected as the control group. Approval from the Institutional Ethics Committee at Bhagwan Mahavir Hospital and Research Centre in Hyderabad, Telangana, was obtained for this study. All the participants provided their consent. The data was collected on various health problems, and reproductive outcome such as fertility, number of pregnancies,

live births, abortions, premature births, stillbirths, and neonatal deaths.

Sample Collection

Blood samples were obtained from both women engaged in beedi rolling and the control group. These samples were then placed into plain vacutainers, and the serum was separated. The Complete Blood Picture (CBP) was assessed utilizing the Lab Life Noble III Analyzer, a hematology analyzer, in both women engaged in beedi rolling and those not involved in such activities. The isolated serum was subsequently employed for the determination of nicotine metabolites.

Estimation of Nicotine Metabolites

The study involved the assessment of five nicotine metabolites—Cotinine, Anabasine, Nornicotine, Nitrosonornicotine (NNN), and 4-(methylnitrosamino)-1-(3-pyridyl)-1 butanone (NNK)—in 320 samples from beedi rollers and 280 samples from individuals not engaged in beedi rolling. The quantification of nicotine metabolites and other toxic components in beedi rollers was conducted through Liquid Chromatography Coupled with Mass Spectrometry (LCMS). All serum samples from both the study and control groups underwent Nicotine metabolite analysis using the Quattro premier XE system (Waters Systems, USA) and the Acquity UPLC system (Waters Systems, USA) as a Front End (LC). Nicotine metabolites were quantified using LC-MS/MS with the Positive ESI Method.

Sample Preparation

Samples were prepared by weighing and transferring 1.0 mg of nicotine metabolites in 1.0 mL of DMSO to achieve a concentration of 2 mg/mL. The concentration standard into a ria vial to create calibration curve standards. The standard was dissolved in 1.000 mL of methanol, resulting in a final concentration of 1.00 mg/mL. Individual metabolites were combined to form a mixed standard. Adequate separation was achieved using an Agilent Zordax-XDB column (C18 2.1 × 50 mm, 3.5 µm). The mobile phase-A consisted of 100% acetonitrile (approximately 1000 mL), while mobile phase B was comprised of approximately 500 mL of HPLC grade water. To this, 126 mg of ammonium formate and 2 mL of formic acid were added, and the volume was adjusted to 1000 mL with water.

Sample Analysis

Retrieved serum blank and study serum samples from the deep freezer and allowed them to reach room temperature. The mixed nicotine metabolites spiking solutions were added to the samples, followed by vortexing to ensure complete mixing. A 20 µL solution of 50% methanol in water was added to a ria vial and labeled as blank. Subsequently, 20 µL of ISTD (Verapamil-2 µg/mL) was added to all pre-labeled ria vials (except blank), and 100 µL of respective CC & QC samples, study samples were added and vortexed. Further, 0.250 mL of acetonitrile was added to all samples, followed by vortexing and centrifugation at 4000 rpm, at 20°C for 10 min. The supernatant layer (0.150 mL) was separated and loaded into auto-injector vials. Finally, 10 µL was injected onto the LC-MS/MS system, and the data were processed for the quantification of metabolites. The data produced in the study underwent analysis utilizing SPSS software along with other statistical tools available online.

Results

The demographic data analysis unveiled notable distinctions in the rates of literacy and income between women engaged in beedi rolling and those not involved in the occupation. Specifically, the women in the beedi rollers group exhibited significantly lower levels of literacy and income in comparison to their counterparts in the non-beedi roller group (Table 1).

Table 1. Demographic data of Beedi Rollers and Control Subjects

Variable	BR (n=320) (%)	NBR (n=280) (%)	X2	P value
Age (Mean ±SD)	37.14±10.30	35.57±9.23	NA	
Age Groups (Years)				
<25	101 (31.56)	107 (22.67)	4.338	0.1143
25-45	158(49.38)	134(49.85)		
>45	61(19.06)	39(27.48)		
Marital Status				
Unmarried	34(10.62)	42 (15.00)	2.58	0.1080
Married	286 (89.38)	238(85.00)		
Educational Status				
Illiterate	130 (56.20)	49(17.50)	69.76	<0.0001
Primary (5th Std)	206 (30.36)	124 (44.29)		
Secondary (10th Std)	44 (13.44)	107 (38.21)		
Occupation			600.0	<0.0001
Beedi Roller	380(100.0)	0(0)		
Other Private Job	0(0)	51 (18.21)		
House wife / Home maker	0(0)	219 (78.21)		
Student/Others	0(0)	10 (3.57)		
Income/Month				
<1000	8 (2.11)	0(0)	205.0	<0.0001
1000-5000	229(76.05)	44 (15.71)		
>5000	7 (1.84)	22 (7.86)		
Not reported	76 (20.00)	214 (76.43)		

The findings on health issues revealed a high prevalence of tuberculosis among individuals engaged in beedi rolling. In the control group, the incidence of tuberculosis was 3.57%, while it escalated to 11.88% among beedi rollers. Additionally, asthma exhibited a notable increase from 4.29% in controls to 15.63% in the beedi roller cohort. The occurrence of shoulder pain also rose from 5.71% in controls to 10.31% among beedi rollers. Likewise, a substantial percentage of health issues, including neck pains (3.57% vs. 12.50%), joint pains (10.71% vs. 16.88%), cough (8.21% vs. 12.19%), eye burning (7.14% vs. 15.31%), headache (17.86% vs. 26.88%), giddiness (6.07% vs. 9.38%), hypertension (7.14% vs. 12.81%), diabetes (5% vs. 8.75%), skin diseases (7.14% vs. 9.06%), and anemia (10.36% vs. 17.81%), were notably higher in beedi rollers compared to control subjects (Table 2).

Table 2 Health problems in Beedi Rollers and control subjects

Variable	BR n=320 (%)	NBR n=280(%)	P value
TB	38(11.88)	10(3.57)	0.0001
Asthma	50(15.63)	12(4.29)	0.0001
Cough	39 (12.19)	23 (8.21)	0.1388
Shoulder pains	33 (10.31)	16(5.71)	0.0513
Neck pains	40 (12.50)	10 (3.57)	0.0001
Joint pains	54 (16.88)	30(10.71)	0.1937
Eye burning	49 (15.31)	20 (7.14)	0.0019
Headache	86(26.88)	50(17.86)	0.0109
Giddiness	30 (9.38)	17 (6.07)	0.1701
Hypertension	41 (12.81)	20(7.14)	0.0296
Diabetes	28 (8.75)	14 (5.00)	0.0791
Skin Diseases	29 (9.06)	20 (7.14)	0.4558
Anaemia	57 (17.81)	29 (10.36)	0.0101

The study also revealed notable alterations in hematological parameters among women engaged in beedi rolling compared to control subjects. Specifically, the mean values of red blood cell (RBC) count (3.77±0.70), hemoglobin (9.14±1.57), white blood cell (WBC) count (8.13±1.14 103/µl), neutrophils (47.22±3.66), and mean corpuscular hemoglobin concentration (MCHC) (31.54±15.42) demonstrated a decrease. Conversely, an increase was observed in lymphocytes (40.18±24.95), hematocrit (36.10±5.50), mean corpuscular volume (MCV) (89.44±10.17), and red cell distribution width coefficient of variation (RDW CV) (14.71±2.23) among beedi rollers compared to the corresponding values in control subjects (RBC: 4.15±0.37, hemoglobin: 12.18±1.99, WBC: 7.12±2.33, neutrophils: 62.82±6.11, MCHC: 34.01±10.10, lymphocytes: 22.81±4.64%, hematocrit: 31.70±4.23, MCV: 44.05±12.58, RDW CV: 12.84±1.49). Application of the Independent t-test in statistical analysis underscored the significance of these observed differences. Specifically, the decrease in RBC count, hemoglobin, WBC, neutrophils, and MCHC, as well as the increase in lymphocytes, hematocrit, MCV, and RDW CV, were deemed statistically significant in the beedi rollers compared to the control subjects (Table 3).

Table 3 Haematological Studies in Beedi Rollers and control subjects

Variable	BR (Mean±SD) n= 320	NBR (Mean±SD) n= 280	P value
Total WBC (10^3/µl)	8.13±1.14	7.12±2.33	<0.0001
Neutrophils (%)	47.22±3.66	62.82±6.11	<0.0001
Lymphocytes (%)	40.18±24.95	22.81±4.64	<0.0001
Eosinophils (%)	1.94± 1.09	2.09±0.83	0.0612
Monocytes (%)	5.88±1.50	6.15±0.98	0.0104
Basophils (%)	0.00±0.00	0.00±0.00	
RBC Count(10^6/µl)	3.77±0.70	4.15±0.37	<0.0001
Haemoglobin (g/dL)	9.14±1.57	12.18±0.99	<0.0001
Haematocrit (%)	36.10±5.50	31.70±4.23	<0.0001
MCV (fL)	89.44±10.17	44.05±12.58	<0.0001
MCH(pg)	29.36±12.08	25.43±1.61	<0.0001
MCHC(g/dL)	31.54±15.42	34.01±10.10	0.0226
RDW CV(%)	14.71±2.32	12.84±1.49	<0.0001
Platelets (103/µl)	299.16±95.13	320.85±76.13	0.0024

Reproductive outcomes were examined in 286 married women engaged in beedi rolling and compared with 238 married women not involved in this occupation. The findings revealed that the infertility rate was higher in the beedi rolling group (4.78%) compared to the control group (1.26%). Additionally, a higher incidence of miscarriages was observed in the beedi rolling group (10.82%) in contrast to the control group (5.23%) (Table 4).

Table 4 Reproductive Outcome in Married Beedi Rollers and Married Non-Beedi Rollers

Variable	BR (n=286) (%)	NBR (n=238) (%)	P value
Infertile	30(4.78)	3(1.26)	<0.0001
Fertile	256(95.22)	235(98.74)	
Pregnancies	536	440	
Live Children	451(84.14)	410 (93.18)	<0.0001
Miscarriage	58(10.82)	23(5.23)	0.0016
Premature Births	11(2.05)	4(0.91)	0.1936
Neonatal Deaths	3(0.56)	1(0.23)	0.6315
Still births	13 (2.43)	2 (0.45)	0.0161

Estimation of nicotine metabolites findings revealed a notable increase in the mean levels of all nicotine metabolites among beedi rollers compared to control subjects. For instance, the cotinine level in control subjects was 1.468 ng/mL, while it escalated to 122.2 ng/mL in beedi rollers. The mean difference between the two groups was 120.7 with a standard error of 14.85, demonstrating a highly significant p-value (<0.0001) between beedi rollers and non-beedi rollers. Similarly, the nor-nicotine mean value was 0.003571 ng/mL in control subjects, increasing to 0.8755 ng/mL in beedi rollers. The mean difference between the groups was 0.8719, with a standard error of 0.1067, indicating high significance ($P < 0.0001$). Anabasine exhibited a mean value of 1.724 ng/mL in controls, rising to 7.294 ng/mL in beedi rollers, with a mean difference of 5.570 and a standard error of 0.4913, showing high significance ($P < 0.0001$) (Table 5).

Table 5 Estimation of Nicotine Metabolites in Beedi rollers and control subjects

Nicotine Metabolite	Controls, n=320 Mean± SEM	Subjects, n= 280 Mean± SEM	Difference between means (± SEM)	95% CI	P Value
Anabasine (ng/mL)	7.294	1.724	5.570±0.4913	4.605 to 6.535	<0.0001
NNN (ng/G)	2.1342	0.12	2.014±0.1899	1.641 to 2.387	<0.0001
NNK (ng/G)	0.352	0.02804	0.3240±0.1038	0.1202 to 0.5278	<0.0001
Nornicotine (ng/mL)	0.8755	0.003571	0.8719±0.1067	0.6624-1.081	<0.0001
Cotinine(ng/mL)	122.2	1.468	120.7±14.85	91.53 to149.85	<0.0001

Furthermore, NNK mean value in non-beedi rollers was 0.02804 ng/g, compared to 0.352 ng/g in beedi rollers, resulting in a mean difference of 0.3240 and a standard error of 0.1038, with a highly significant p-value of <0.0001. NNN mean value in non-beedi rollers was 0.12 ng/g, whereas in beedi rollers, it was 2.1342 ng/g, revealing a mean difference of 2.014 and a standard error of 0.1899, with a highly significant p-value <0.0001. The statistical analysis, conducted using an independent t-test, confirmed that the increase in all metabolites in beedi rollers was statistically significant when compared with the control subjects (Figure 1&2).

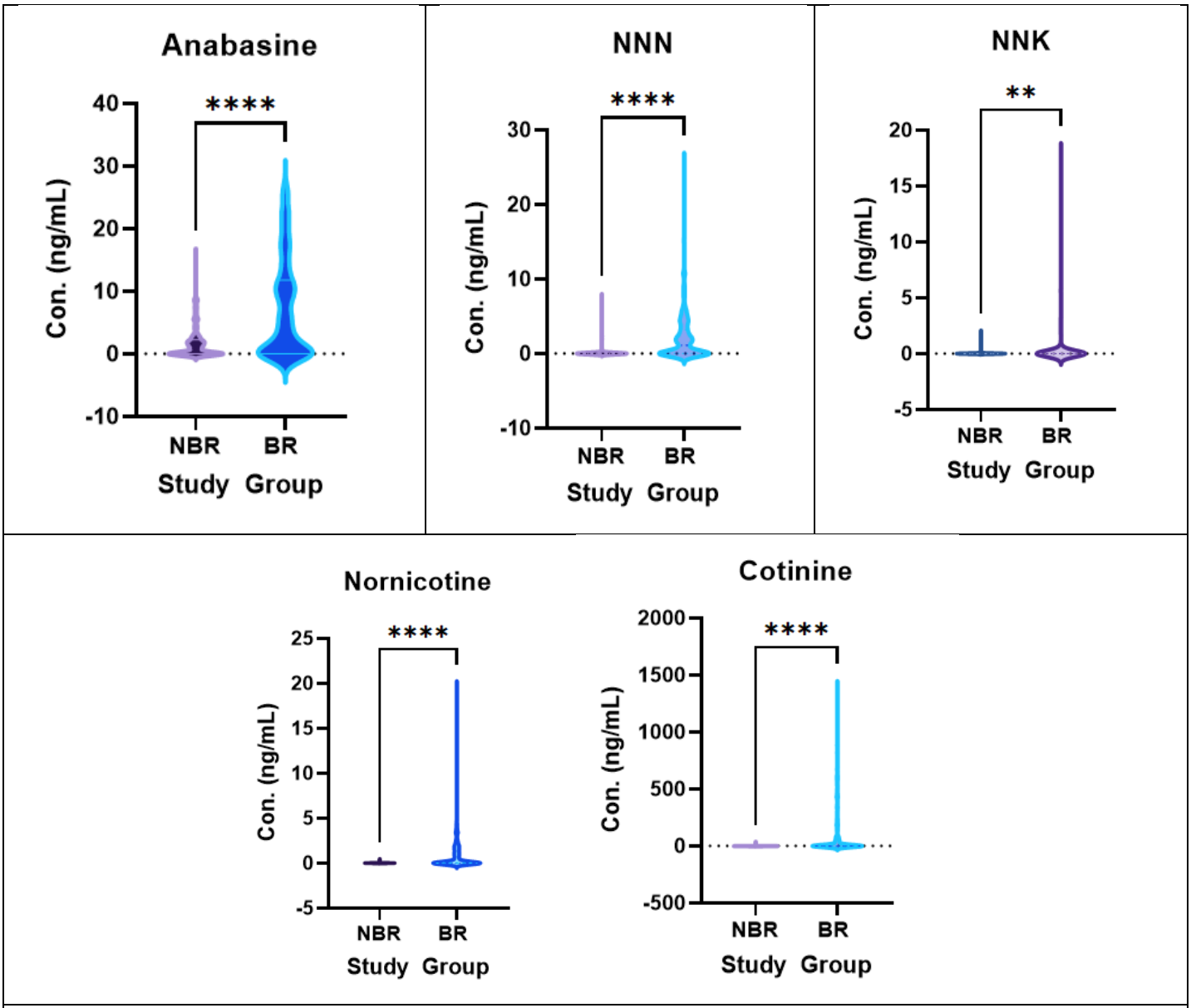

Figure 1. Estimation of Nicotine metabolite concentrations in the Study group (Beedi Rollers (BR) and Non- beedi rollers (NBR)

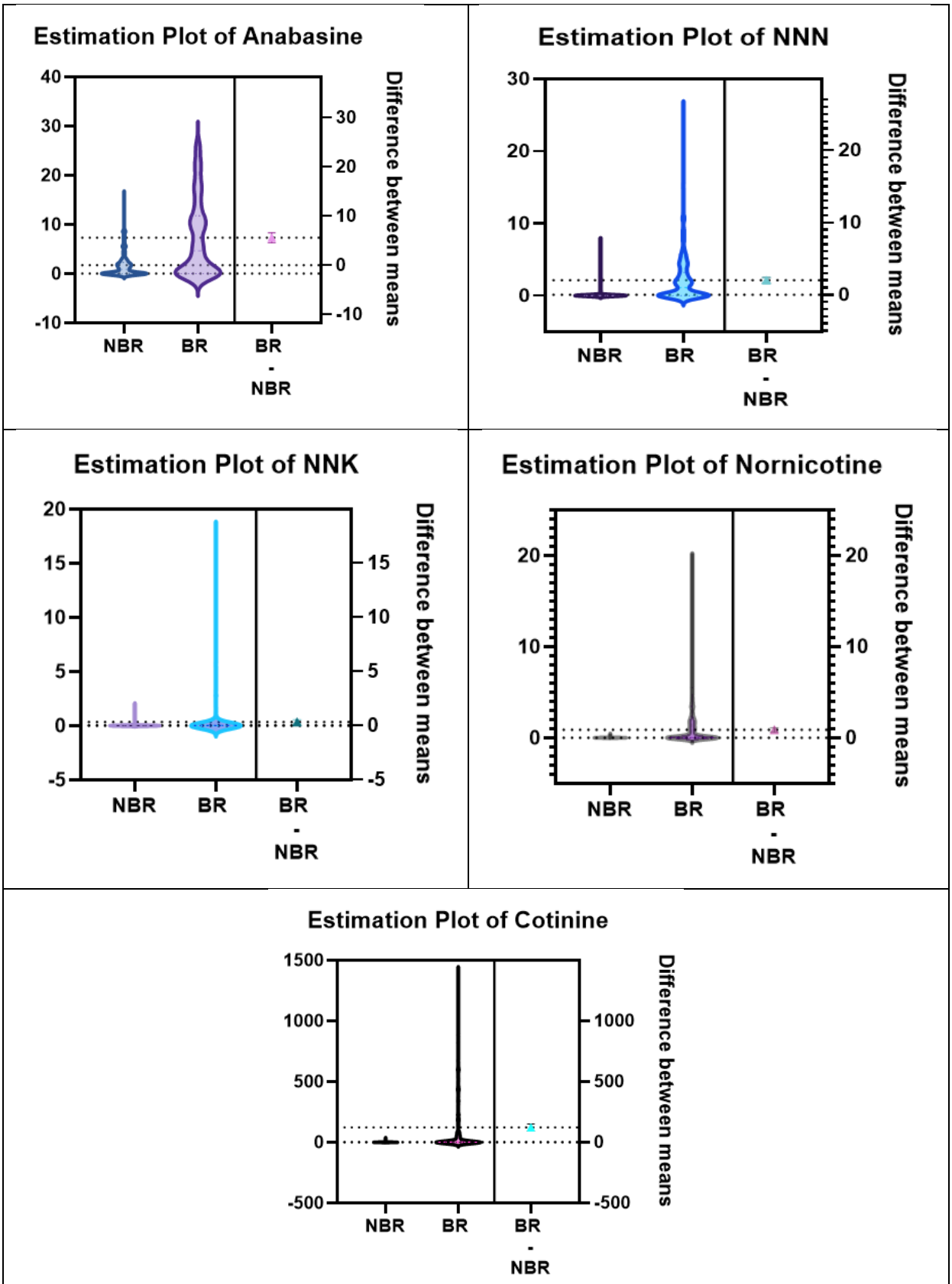

Figure 2. Estimated plots of mean difference between the study groups of targeted nicotine metabolites

Additionally, the study calculated the mean difference in both groups, demonstrating variations in all the metabolites. A Heat Map was created to assess the intensity of nicotine levels in all subjects (BR and NBR) across various nicotine metabolites (Cotinine, Anabasine, Nornicotine, NNN, and NNK). Among beedi rollers, Cotinine, Anabasine, and NNN exhibited high intensity, while Anabasine was slightly higher in the NBR group. Nevertheless, the levels were markedly higher in beedi rollers compared to the non-beedi roller group (Figure 3).

In the study group, the order of estimated nicotine quantification levels is as follows: Cotinine > Anabasine > Nornicotine > NNN > NNK.

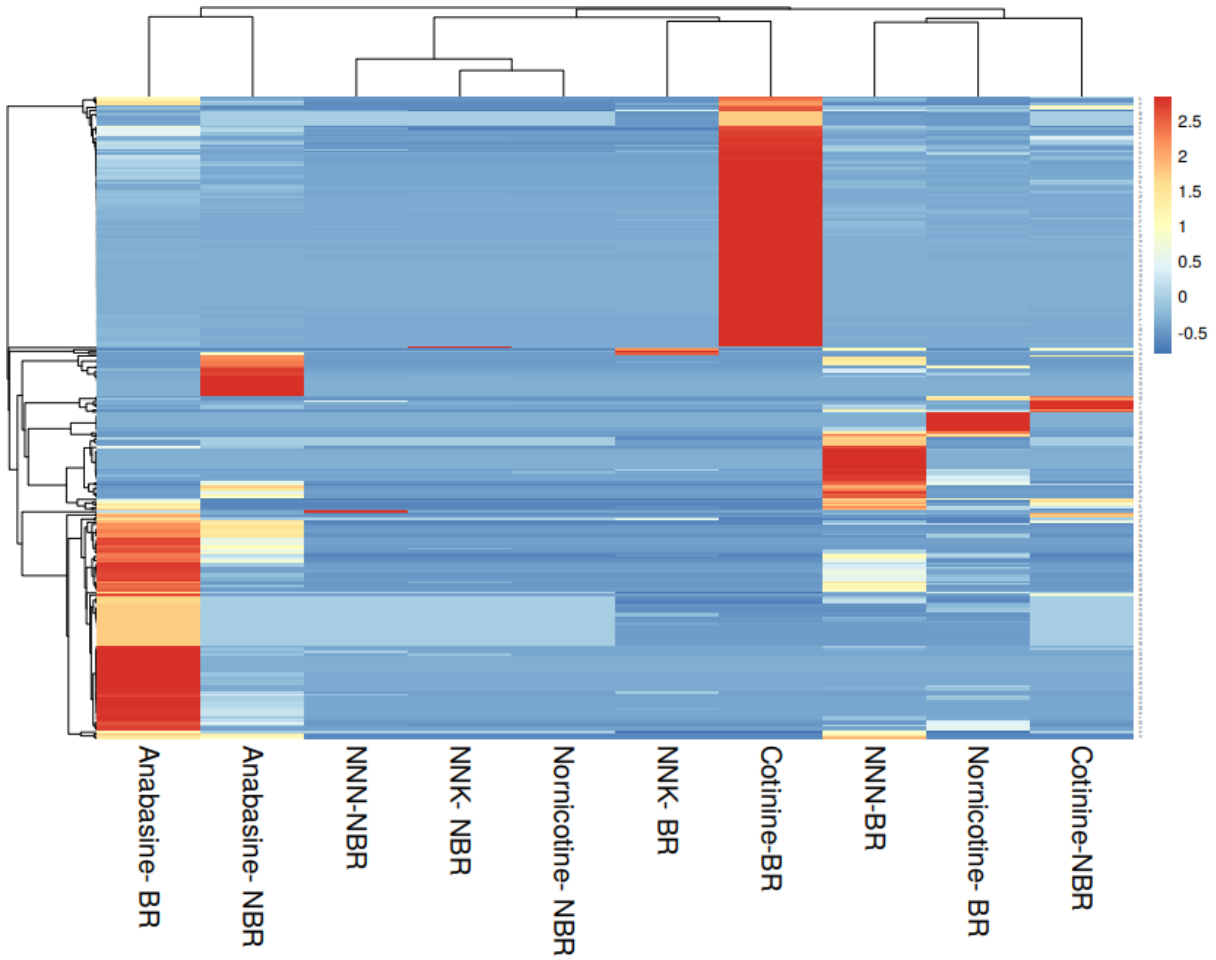

Figure 3. Heat map for Nicotine metabolites in the study groups (i.e, Beedi rollers (BR) and Non-beedi rollers (NBR)

Discussion

Women in the beedi rolling industry, spending prolonged hours surrounded by tobacco dust, often experience various health issues[1]. Given the substantial number of rural women engaged in this industry, understanding the effects of occupational tobacco exposure on health becomes imperative. Nicotine, a potent alkaloid with well-documented systemic side effects and carcinogenic potential, was initially extracted from tobacco by German physicians Wilhelm Heinrich Posselt and Karl Ludwig Reimann. In its pure form, nicotine is a clear liquid with a distinctive odor that turns brown upon exposure to air. Possessing water solubility, it readily separates from organic solvents. This amine, comprising pyridine and pyrrolidine rings, is dibasic, and its absorption in the human body

depends on the pH of the solution. Nicotine absorption can occur through various routes such as oral mucosa, lungs, skin, or the gastrointestinal tract. The pH of a solution influences the concentration of uncharged lipophilic nicotine, allowing it to actively traverse biological membranes[2].

Upon ingestion, nicotine undergoes absorption and metabolic processes in the liver. In phase I, microsomal oxidation results in the formation of metabolites like cotinine, nornicotine, demethyl cotinine, trans-3-hydroxycotinine, and d-(3-pyridyl)-g-methylaminobutyric acid. Phase II involves N'- and O'-glucuronidation of these metabolites, leading to excretion via urine, feces, bile, saliva, and sweat. Approximately 5-10% of elimination involves renal excretion of unchanged nicotine, with potential reabsorption from the bladder under high urinary pH conditions[3]. There is evidence suggesting in vivo nitrosation of nicotine, leading to the formation of highly carcinogenic compounds such as N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Inflammation in the oral cavity increases the risk of endogenous nitrosation[4]. Nicotine exerts its effects on various organ systems through three major mechanisms; 1. Ganglionic transmission 2. Activation of nicotinic acetylcholine receptors (nAChRs) on chromaffin cells via catecholamines and 3. Central nervous system (CNS) stimulation of nAChRs[5].

In the female reproductive system, nicotine exerts an impact on the menstrual cycle by inhibiting 21-hydroxylase, leading to a hypoestrogenic state. This inhibition redirects metabolites towards androgen formation, resulting in chronic anovulation and irregular menstrual cycles. Additionally, nicotine has been linked to the predisposition of the endometrium to inappropriate cytokine production, contributing to irregular bleeding[6]. Evidence consistently suggests that the increase in follicle-stimulating hormone levels and the decrease in estrogen and progesterone associated with cigarette smoking in women are, at least in part, attributed to the effects of nicotine on the endocrine system[7]. Nicotine's influence extends to oocytes, affecting the ovaries and altering oocyte production, as demonstrated in various animal studies. Nicotine-treated oocytes exhibit nonspherical shapes with rough surfaces and torn, irregular zona pellucida. Furthermore, nicotine induces disturbances in oocyte maturation and reduces blood flow to the oviducts, thereby impairing fertilization[8].

A study was conducted on the female beedi rollers in Patna, Bihar, India, with the aim of assessing the impact of beedi rolling on health. The investigation revealed that over 70% of the beedi rollers experienced health issues related to the eyes, gastrointestinal system, and nervous system. Additionally, more than 50% of the participants reported respiratory problems, primarily manifesting as throat burning and cough. Osteological problems were prevalent in over 75% of the respondents. Laboratory analyses indicated significant reductions in total red blood cell (RBC), white blood cell (WBC), and platelet counts among beedi rollers compared to the control group. The differential leucocyte count demonstrated elevated lymphocytes and eosinophils, along with reduced neutrophils and monocytes in the beedi rollers when compared to the control group. Hemoglobin levels were observed to be lower in beedi rollers in comparison to the control group. Furthermore, the concentration of serum glutamic pyruvic transaminase (SGPT or ALT), an indicator of liver dysfunction, was significantly higher in the beedi rollers as opposed to the control group[9]. The hematological investigations of present study disclosed, notably a statistically significant decline in red blood cell (RBC) count, hemoglobin, white blood cell (WBC) count, neutrophils, and mean corpuscular hemoglobin concentration (MCHC) among beedi rollers. Conversely, there was a statistically significant increase in lymphocytes, hematocrit, mean corpuscular volume (MCV), and

red cell distribution width coefficient of variation (RDW CV) in comparison to the control subjects.

In the urban areas of Mangalore, women involved in beedi rolling frequently encounter musculoskeletal problems, with eye and respiratory issues being the subsequent common health concerns[10]. In research conducted by Surya Prabha and Shantha Kumari on the morbidity profile of women beedi workers in the Urban Slum of Kurnool Town, Andhra Pradesh, it was found that the prevalent health issues among these women primarily included musculoskeletal problems, followed by eye problems and respiratory issues[11]. A study conducted on the occupational morbidity of women beedi workers in rural areas of Nizamabad district, Telangana, revealed noteworthy findings. A substantial proportion of the workers exhibited chronic health issues, including musculoskeletal problems (50%), gynecological problems (31%), respiratory morbidity (27%), hypertension (25%), malnutrition (20%), and diabetes mellitus (2.65%) (12). While, the results from the present study indicated an elevated incidence of tuberculosis, asthma, shoulder pain, neck pains, joint pains, cough, eye burning, headache, giddiness, hypertension, diabetes, skin diseases, and anemia among individuals involved in beedi rolling when compared to the control subjects. The results also revealed higher rates of infertility, miscarriage, and stillbirths, coupled with a decrease in live births among women involved in beedi rolling as compared to the control group, which were in consistent with our earlier study[13].

A study investigating the impact of nicotine exposure during pregnancy on birth weight among women engaged in beedi rolling revealed that maternal exposure to nicotine through this occupation is correlated with a decrease in birth weight[14]. To the best of our knowledge, our research represents the first attempt in India to investigate the influence of tobacco exposure on health of women involved in beedi rolling in rural Telangana by assessing nicotine metabolites through Liquid Chromatography-Mass Spectrometry Analysis. The unique contribution of our study lies in shedding light on the health implications of tobacco exposure among this specific demographic, utilizing LC-MS analysis for a comprehensive understanding. The assessment of nicotine metabolites unveiled a significant elevation in the mean levels among beedi rollers in contrast to the control subjects. Notably, within the beedi rollers group, high intensity was observed in Cotinine, Anabasine, and NNN. Additionally, Anabasine demonstrated a slightly elevated presence in the non-beedi rollers (NBR) group. The study's results constitute a crucial reservoir of knowledge regarding nicotine metabolite levels and their repercussions on the overall health of women involved in beedi rolling. The findings of the study serve as a crucial source of information on nicotine metabolites levels and its impact on overall health of beedi rolling women.

Conclusion

The research highlights the influence of nicotine metabolites on overall health of women engaged in beedi rolling. There is a necessity to raise awareness among these women regarding the occupational risks they encounter. Moreover, there is an appeal for the enforcement of policies that hold employers accountable for reducing exposures and fostering enhancements in the overall health of this occupational cohort.

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