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# Association between ECG Abnormalities and Hookah and Cigarette Smoking in the MASHAD Cohort Study Subjects

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ABSTRACT

**Introduction:** Tobacco use, including cigarette and hookah smoking, is a major public health issue due to its association with cardiovascular disease (CVD). Cigarette and hookah smoking introduce harmful substances that lead to atherosclerosis, endothelial dysfunction, and myocardial ischemia, resulting in significant cardiovascular morbidity and mortality. In this study, we aimed to assess the association between hookah and cigarette smoking and ECG patterns using Minnesota Coding (MC) system in a large-scale population.

**Methods:** This study utilized data from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort, involving 9,704 participants aged 35-65 years. Demographic data, physical measurements, smoking habits, and medical histories were collected. Resting 12-lead ECGs were analyzed using the MC system to identify minor and major ECG abnormalities. Statistical analyses included binary logistic regression adjusted for sex, BMI, education, and employment status, as well as chi-squared tests.

**Results:** The final analysis included 8,821 participants. Cigarette users (92.3% male) had significantly lower BMI and higher employment rates compared to non-smokers, whereas hookah smokers (90.2% female) had higher BMIs and were predominantly retirees. Cigarette smokers exhibited a higher prevalence of minor ECG abnormalities (25.6% vs. 20.2%, p = 0.001), particularly ST-segment elevation, left axis deviation, sinus bradycardia, and high amplitude P-waves. Logistic regression confirmed significant associations for sinus bradycardia (OR: 1.600, 95% CI: 1.127-2.271, p = 0.009) and high amplitude P-waves (OR: 4.775, 95% CI: 1.771-12.880, p = 0.002). Hookah smokers had higher rates of left ventricular hypertrophy plus ST-T abnormalities (7.9% vs. 5.0%, p = 0.027) and a significantly lower prevalence of sinus tachycardia (0.3% vs. 1.6%, p = 0.042).

**Conclusion:** Cigarette and hookah smoking are associated with specific ECG abnormalities, suggesting significant cardiovascular effects. The persistence of certain abnormalities after adjustment underscores the long-term impact of smoking on cardiac function. Further research is needed to elucidate the mechanisms and mitigate the cardiovascular risks associated with various forms of tobacco use.

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## Introduction

Tobacco use, encompassing both cigarette and hookah smoking, remains a major public health concern due to its well-documented association with cardiovascular disease (CVD) and changes in electrocardiogram (ECG) patterns (1-6). Tobacco smoking, irrespective of the form, introduces a variety of harmful substances into the body, including nicotine, tar, carbon monoxide, and various carcinogens (7, 8), all of which play a role in cardiovascular morbidity and mortality (9).

Cigarette smoking is a leading form of tobacco consumption worldwide that is extensively studied for its cardiovascular implications (10-12). Cigarette smoke contains numerous harmful chemicals that induce oxidative stress (13), inflammation (14), and vascular injury (15), leading to increased risks of coronary artery disease (CAD) (16), myocardial infarction (16), and stroke (17). Smokers show an imbalance of lipid profile (18), fostering an atherogenic lipid profile (19).

Hookah smoking, traditionally rooted in Middle Eastern cultures, has gained popularity among youth globally because of its perceived social acceptability and the misconception of being a safer alternative to cigarettes (20-23). However, emerging evidence suggests that hookah smoking poses similar, or even more risks to cardiovascular health as cigarette smoking. A typical hookah session can expose the smoker to substantially elevated levels of smoke and toxicants compared to a single cigarette (24). Hookah smoke has been associated with oxidative stress within the vasculature, arterial hypertension, and endothelial dysfunction (24).

One way to evaluate the cardiovascular effects of hookah and cigarettes is by analysis of ECG patterns (25, 26). The ECG is a non-invasive test frequently used to evaluate cardiac function and disease. It is an affordable and easily available instrument in cardiology that offers useful information on the heart's electrical activity (27). Hookah smoking causes immediate ECG alterations that may predict future cardiovascular conditions (26). Also, smoking cigarettes is significantly correlated with ECG results (28). The Minnesota Coding (MC) System provides an objective method for categorizing ECG patterns that may be used in investigations and subsequent statistical analyses (29). In this study, we aimed to assess the association between hookah and cigarette smoking and ECG patterns using MC in a large-scale population, which to our knowledge, is of the few works conducted on a Persian population that investigates both hookah and cigarette.

## Methods

### *1. Study Design and Participants*

A total of 9,704, subjects age 35- to 65 from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort study phase one, previously described in studies (30, 31), were enrolled in the investigation. Participants were chosen from three urban areas in Mashhad according to the MASHAD study protocol. Data collected included demographic information, physical exercise, anthropometric measurements, nutritional intakes, smoking habits, and past medical history. Fasting blood samples were taken from all participants to measure fasting blood glucose (FBG) and lipid profiles. Diabetes was defined as FBG ≥126 mg/dL or a prior diagnosis, while hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP ≥90 mmHg, or a prior diagnosis. CVD was confirmed by a cardiologist based on a CVD risk-related questionnaire, a resting 12-lead ECG, and additional tests if necessary. The participants were divided into three groups base on their daily smoking habits (including cigarettes and hookah). All participants provided informed consent for the collection of their anonymized clinical data, and all procedures were approved by Mashhad University of Medical Sciences in Iran.

### *2. Resting 12-lead ECG and Minnesota Coding System*

A resting 12-lead ECG was recorded for each participant, scanned, and digitally stored. Standard ECGs (25 mm/s speed, 10 mm/mV voltage) were coded using the MC system (32), totaling 9035 cases. Ten trained medical students classified minor and major abnormalities using a dedicated digital

platform following the Minnesota manual (32). Inter-observer and intra-observer agreement were 0.97 and 0.99, with variability rates of 10% and 5.3%, respectively. Three cardiologists reviewed 5% of all ECGs. Overall, 94% of the codes generated by the trained staff matched those generated by the cardiologists. The minimum and maximum QT intervals were corrected using Bazett's formula (QTc = QT/RR^1/2). Major ECG abnormalities included major Q wave abnormalities, left ventricular hypertrophy (LVH) with ST-T abnormalities, major isolated ST-T abnormalities, atrial fibrillation (AF) or flutter, minor Q wave abnormalities with ST-T abnormalities, Wolff-Parkinson-White (WPW), right bundle branch block (RBBB), complete or intermittent left bundle branch block (LBBB), RBBB with left anterior hemiblock, supraventricular tachycardia (SVT), second-degree atrioventricular block (AVB2), third-degree atrioventricular block (AVB3), ventricular fibrillation or ventricular asystole, nonspecific intraventricular block, Brugada pattern, major QT index≥116% while QT Index = [QT interval × (HR+100)/656] (33), and artificial pacemaker. Minor abnormalities were defined as minor isolated Q/QS waves. high R wave (right ventricular), minor ST/T abnormalities, incomplete RBBB, right axis deviation, left axis deviation, ST-segment elevation, long PR interval, incomplete LBBB, minor QT prolongation (QT index≥112%), short PR interval, premature supraventricular beats, high R wave (left ventricular), premature ventricular beats, fragmented QRS, premature combined beats, supraventricular rhythm persistent, sinus tachycardia, sinus bradycardia, low voltage QRS, wandering atrial pacemaker, left atrial enlargement (LAE), and high amplitude P wave. Participants with both minor and major abnormalities were categorized as having major abnormalities, while those without minor or major ECG abnormalities were considered to have marginal or no abnormalities, indicating a normal ECG (34).

### *3. Statistical Analysis*

Data analyses were conducted using SPSS version 21. Results are presented as absolute numbers (n), mean ± standard deviation, and frequencies as percentages. The chi-squared test was used to compare ECG abnormalities among different groups of daily cigarette and hookah smokers. Additionally, multiple logistic regression was applied to the data with subsequent adjustments for sex, BMI, academic degree, and job status.

## Results

After excluding participants with a history of pre-existing CVD and those who consumed tobacco in the form of both hookah and cigarettes, a total of 8821 individuals entered the analysis, including 7800 non-smokers, 716 cigarette smokers, and 305 hookah smokers. Table 1 illustrates baseline characteristics categorized by smoking status. The mean age was 47.96±8.24 years for non-smokers, 47.84±7.64 years for cigarette smokers, and 48.55±8.13 years for hookah smokers. Cigarette smokers had a significantly higher proportion of males (92.3%) compared to non-smokers (35.9%, $p < 0.001$), while hookah smokers had a significantly higher proportion of females (90.2%) compared to non-smokers (64.1%, $p < 0.001$). BMI was significantly lower in cigarette smokers (25.27 kg/m2) compared to non-smokers (28.09 kg/m2, $p < 0.001$), whereas hookah smokers had a significantly higher BMI (28.97 kg/m2) compared to non-smokers ($p < 0.001$). Hookah smokers predominantly comprised retired individuals (84.3%), with a smaller proportion being employed (14.4%) and 1.3% being unemployed. Conversely, cigarette smokers were mostly employed (71.1%), followed by retirees (15.4%) and those unemployed (13.5%). Non-smokers comprised mostly retirees (55.2%), followed by employed individuals (35.0%) and unemployed participants (9.7%). The prevalence of cigarette smoking among individual with different educational degrees is almost the same, but hookah smokers significantly tend to have primary school degrees or be illiterate .

Table 2 presents the frequency of ECG abnormalities among different smoking groups. Cigarette smokers had a significantly higher rate of minor abnormalities (25.6%) compared to non-smokers (20.2%, $p = 0.001$, OR: 1.359, 95% CI: 1.139-1.622).

**Table 1.** Baseline characteristics according to smoking status.

| ECG abnormalities | | Daily Smoking | | | P - value |
|---|---|---|---|---|---|
| | | No (7800) | Cigarette (716) | Hookah (305) | |
| Age (year) | | 47.96±8.24 | 47.84±7.64 | 48.55±8.13 | 0.422 |
| Sex | Male | 2803 (35.9) | 661 (92.3) | 30 (9.8) | <0.001 |
| | Female | 4997 (64.1) | 55 (7.7) | 275 (90.2) | |
| BMI (kg/m2) | | 28.09±4.67 | 25.27±4.56 | 28.97±4.95 | <0.001 |
| Job status | Unemployment | 760 (9.7) | 97 (13.5) | 4 (1.3) | <0.001 |
| | Employment | 2730 (35.0) | 509 (71.1) | 44 (14.4) | |
| | Retired | 4306 (55.2) | 110(15.4) | 257 (84.3) | |
| Degree | Illiterate | 926 (11.9) | 70 (9.8) | 124 (40.7) | <0.001 |
| | Primary | 3146 (40.5) | 253 (35.3) | 145 (47.5) | |
| | High school | 2777 (35.8) | 307 (42.9) | 35 (11.5) | |
| | Diploma and above | 914 (11.8) | 86 (12.0) | 1 (0.3) | |

Categorical variables were reported as number (percent) and categorical variables reported as mean ± standard deviation.

They were also more likely to show high amplitude P waves (1.3% vs. 0.3%, p < 0.001, OR: 3.806, 95% CI: 1.777-8.154), ST-segment elevation (7.3% vs. 4.6%, p = 0.002, OR: 1.614, 95% CI: 1.194-2.181), sinus bradycardia (6.6% vs. 2.5%, p < 0.001, OR: 2.784, 95% CI: 2.004-3.867), and left axis deviation (5.7% vs. 3.6%, p = 0.004, OR: 1.631, 95% CI: 1.165-2.285). In contrast, the prevalence of major isolated ST-T abnormalities (2.4% vs. 4.6%, p = 0.002, OR: 0.507, 95% CI: 0.310-0.830) and LVH with accompanying ST-T changes (2.8% vs. 5.0%, p = 0.008, OR: 0.521, 95% CI: 0.331-0.822) was significantly lower among smokers than non-smokers. Moreover, long PR interval (0.6% vs. 0.2%, p = 0.122) and Brugada pattern (0.7% vs. 0.3%, p = 0.054, OR: 2.736, 95% CI: 1.024-7.311) showed a higher prevalence and sinus tachycardia (1.0% vs. 1.6%, p = 0.174, OR: 0.592, 95% CI: 0.275-1.271) showed a lower prevalence in cigarette smokers compared to non-smokers, but were not significant. Table 3 shows the ORs obtained by the logistic regression for the correlation of ECG abnormalities with smoking status. After adjustment, cigarette smoking showed a significant association with high amplitude P waves (OR: 4.775, 95% CI: 1.771-12.880, p = 0.002) and sinus bradycardia (OR: 1.600, 95% CI: 1.127-2.271, p = 0.009). Also, ST-segment elevation (OR: 0.753, 95% CI: 0.550-1.030, p = 0.076) was inversely associated with cigarette smoking.
Individuals who smoked hookah showed a significantly higher prevalence of LVH with ST-T abnormalities (7.9% vs. 5.0%, p = 0.027, OR: 1.606, 95% CI: 1.047-2.463) and a significantly lower incidence of sinus tachycardia (0.3% vs. 1.6%, p = 0.042, OR: 0.197, 95% CI: 0.027-0.415) compared to those who did not smoke.

Additionally, hookah users had an increased rate of minor ST/T abnormalities (4.6% vs. 3.2%, p = 0.163) and major abnormalities (17.0% vs. 14.5%, p = 0.165), which were not statistically significant. However, according to the logistic regression, there was no significant association between hookah smoking and sinus tachycardia (OR: 0.142, 95% CI: 0.020-1.026, p = 0.053) or sinus bradycardia (OR: 1.645, 95% CI: 0.782-3.458, p = 0.189).

## Discussion

### Study Summary

The study examined the baseline characteristics and prevalence of ECG abnormalities in a cohort of 8,821 participants, categorized by their smoking status into non-smokers, cigarette smokers, and hookah smokers. The age difference among groups was not significant. Cigarette smokers demonstrated a significant male predominance, while hookah smokers showed a female predominance. Significant differences in BMI, employment status, and educational attainment were found between cigarette and hookah users. Additionally, several significant minor and major ECG abnormalities were found in these two groups.

**Table 2:** Prevalence of ECG abnormalities according to smoking status.

| Minnesota Code abnormalities | Daily Smoking | | | P value comparing Cigarette smokers and Non-smokers | P value comparing Hookah smokers and Non-smokers |
|---|---|---|---|---|---|
| | No (N=7796) | Cigarette (N=715) | Hookah (N=304) | | |
| Minor abnormalities | 1537 (20.2) | 183 (25.6) | 58 (19.0) | 0.001 | 0.623 |
| Minor isolated Q/QS waves | 375 (4.8) | 36 (5.0) | 14 (4.6) | 0.792 | 0.862 |
| Minor ST/T abnormalities | 246 (3.2) | 17 (2.4) | 14 (4.6) | 0.249 | 0.163 |
| High R waves (left ventricular) | 60 (0.8) | 3 (0.4) | 4 (1.3) | 0.212 | 0.220 |
| High R waves (right ventricular) | 10 (0.1) | 1 (0.1) | 0 (0.0) | 0.620 | 0.681 |
| ST segment elevation | 361 (4.6) | 52 (7.3) | 8 (2.6) | 0.002 | 0.099 |
| Incomplete RBBB | 8 (0.1) | 0 (0.0) | 0 (0.0) | 0.495 | 0.736 |
| Incomplete LBBB | 24 (0.3) | 4 (0.6) | 1 (0.3) | 0.205 | 0.617 |
| Minor QT prolongation | 309 (4.0) | 32 (4.6) | 12 (4.0) | 0.495 | 0.958 |
| Short PR interval | 12 (0.2) | 0 (0.0) | 0 (0.0) | 0.348 | 0.631 |
| Long PR interval | 19(0.2) | 4 (0.6) | 2 (0.7) | 0.122 | 0.186 |
| Left axis deviation | 280 (3.6) | 41 (5.7) | 11 (3.6) | 0.004 | 0.988 |
| Right axis deviation | 22 (0.3) | 1 (0.1) | 1 (0.3) | 0.412 | 0.587 |
| Premature beats (supra ventricular) | 22 (0.3) | 2 (0.3) | 2 (0.7) | 0.672 | 0.228 |
| Premature beats (ventricular) | 92 (1.2) | 6 (0.8) | 4 (1.3) | 0.272 | 0.491 |
| Premature beats (combined) | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0.916 | 0.962 |
| Wandering atrial pacemaker | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0.916 | 0.962 |
| Sinus tachycardia | 128 (1.6) | 7 (1.0) | 1 (0.3) | 0.174 | 0.042 |
| Sinus bradycardia | 192 (2.5) | 47 (6.6) | 8 (2.6) | <0.001 | 0.859 |
| Supraventricular rhythm persistent | 2 (0.0) | 1 (0.1) | 0 (0.0) | 0.232 | 0.926 |
| Low voltage QRS | 137 (1.8) | 15 (2.1) | 3 (1.0) | 0.296 | 0.221 |
| High amplitude P wave | 26 (0.3) | 9 (1.3) | 0 (0.0) | <0.001 | 0.368 |
| Left atrial enlargement (LAE) | 177 (2.3) | 13 (1.8) | 7 (2.3) | 0.432 | 0.976 |
| Fragmented QRS | 124 (1.6) | 15 (1.9) | 22 (2.2) | 0.307 | 0.338 |
| Early repolarization | 82 (1.1) | 11 (1.5) | 3 (1.0) | 0.232 | 0.602 |
| Major abnormalities | 1132 (14.5) | 93 (13.0) | 53 (17.0) | 0.266 | 0.165 |
| Major Q wave abnormalities (Old prevalent MI) | 492 (6.3) | 39 (5.4) | 25 (8.2) | 0.205 | 0.185 |
| Minor Q wave abnormalities plus ST-T abnormalities (possible old MI) | 30 (0.4) | 2 (0.3) | 2 (0.7) | 0.488 | 0.340 |
| Major Isolated ST-T abnormalities | 357 (4.6) | 17 (2.4) | 21 (6.9) | 0.002 | 0.061 |
| Complete or intermittent LBBB | 163 (2.1) | 18 (2.5) | 7 (2.3) | 0.451 | 0.806 |
| Complete or intermittent RBBB | 20 (0.3) | 2 (0.3) | 0 (0.0) | 0.908 | 0.464 |
| Nonspecific intraventricular block | 20 (0.3) | 2 (0.3) | 0 (0.0) | 0.563 | 0.464 |
| RBBB with left anterior hemiblock | 1 (0.0) | 0 (0.0) | 0 (0.0) | 0.916 | 0.962 |
| Brugada pattern | 20 (0.3) | 5 (0.7) | 0 (0.0) | 0.054 | 0.464 |
| Left ventricular hypertrophy plus ST-T abnormalities | 392 (5.0) | 20 (2.8) | 24 (7.9) | 0.008 | 0.027 |
| Major QT prolongation | 133 (1.7) | 15 (2.1) | 6 (2.0) | 0.437 | 0.433 |
| Atrial Fibrillation or Flutter | 5 (0.1) | 0 (0.0) | 0 (0.0) | 0.645 | 0.825 |
| Second-degree AV block (AVB2) | 3 (0.0) | 0 (0.0) | 0 (0.0) | 0.600 | 0.891 |
| Ventricular fibrillation | 3 (0.0) | 0 (0.0) | 0 (0.0) | 0.600 | 0.891 |

Variables were reported as number (percent).

## Demographic Interpretation

### *Relationship between BMI and Smoking Status*

Our results show that cigarette and hookah smokers had significantly lower and higher BMIs, respectively, compared to non-smokers. Past studies on the correlation between cigarette smoking and weight have yielded conflicting results (35). Studies have shown that active nicotine consumption results in reduced caloric intake and appetite in addition to increasing metabolic rate,

particularly in men (35, 36). Studies done on adolescent populations show that one of the greatest predisposing factors for initiating smoking is obesity (35). Conversely, other studies showed that this weight loss was only observed in the short term and that long-term heavy smokers had a higher body weight due to other negative risk behaviors, such as poor diets and sedentary lifestyles (37). Moreover, there is a consensus that cessation of smoking leads to weight gain, with long-term abstinence causing BMI to revert to values equivalent to that of never-smokers (38). In general, most cross-sectional studies have shown that cigarette smokers tend to weigh on average less than the general population, through the effects of nicotine on metabolic hormones, neuropeptides, and adipokines, and by reducing intake and increasing energy expenditure and fat oxidation (39). Hookah smoking, in contrast, is seen to be associated with obesity regardless of gender (40). Chronic hookah use is also positively associated with metabolic syndrome, including diabetes and dyslipidemia (41, 42). In conclusion, the results of this study align with various past literature on this topic, indicating that cigarette and hookah smoking significantly affect weight and BMI.

### *Relationship Between Employment and Smoking Status*

Our results showed that cigarette smokers were typically employed, while hookah and non-smokers were generally retirees. These findings were statistically significant between the groups. Past studies have shown that various socioeconomic factors including housing, education, income, car ownership, and employment can act as predictors of smoking status. However, similar to BMI, there have been mixed results in assessing the correlation between employment and cigarette smoking.

**Table 3.** Association of ECG abnormalities with smoking status.

| | | Crude model | | | Adjusted model* | | |
|---|---|---|---|---|---|---|---|
| **ECG abnormalities** | | **OR** | **95%CI** | **P– value** | **OR** | **95%CI** | **P– value** |
| **Minor abnormalities** | Cigarette | 1.359 | 1.139-1.622 | 0.001 | 1.077 | 0.891-1.301 | 0.444 |
| | Hookah | 0.930 | 0.695-1.244 | 0.623 | 0.967 | 0.718-1.303 | 0.824 |
| **ST segment elevation** | Cigarette | 1.614 | 1.194-2.181 | 0.002 | 0.753 | 0.550-1.030 | 0.076 |
| | Hookah | 0.555 | 0.273-1.129 | 0.104 | 1.007 | 0.484-2.093 | 0.986 |
| **Left axis deviation** | Cigarette | 1.631 | 1.165-2.285 | 0.004 | 1.260 | 0.878-0.810 | 0.210 |
| | Hookah | 1.005 | 0.544-1.856 | 0.988 | 1.091 | 0.582-2.047 | 0.786 |
| **Sinus tachycardia** | Cigarette | 0.592 | 0.275-1.271 | 0.179 | 0.876 | 0.385-0.991 | 0.751 |
| | Hookah | 0.197 | 0.027-0.415 | 0.106 | 0.142 | 0.020-1.026 | 0.053 |
| **Sinus bradycardia** | Cigarette | 2.784 | 2.004-3.867 | <0.001 | 1.600 | 1.127-2.271 | 0.009 |
| | Hookah | 1.067 | 0.521-2.186 | 0.859 | 1.645 | 0.782-3.458 | 0.189 |
| **High amplitude P wave** | Cigarette | 3.806 | 1.777-8.154 | 0.001 | 4.775 | 1.771-12.880 | 0.002 |
| | Hookah | - | - | - | - | - | - |
| **Major Isolated ST-T abnormalities** | Cigarette | 0.507 | 0.310-0.830 | 0.007 | 0.840 | 0.497-1.419 | 0.515 |
| | Hookah | 1.542 | 0.977-2.432 | 0.063 | 1.173 | 0.736-1.872 | 0.502 |
| **Brugada pattern** | Cigarette | 2.736 | 1.024-7.311 | 0.045 | 1.234 | 0.440-3.455 | 0.689 |
| | Hookah | - | - | - | - | - | - |
| **Left ventricular hypertrophy plus ST-T abnormalities** | Cigarette | 0.521 | 0.331-0.822 | 0.005 | 0.744 | 0.459-1.207 | 0.230 |
| | Hookah | 1.606 | 1.047-2.463 | 0.030 | 1.244 | 0.802-1.929 | 0.329 |

* Adjusted for sex, BMI, job and degree; Reference: no smoking

One cross-sectional study found a greater proportion of smokers to be unemployed, while another study revealed that although employment was associated with increased odds of smoking, it was a poor predictor (43, 44). Other studies have shown a positive association between workplace stress, job strain, and cigarette smoking (45). Moreover, work loss and income decrease were found to not significantly affect quit intention or success (46). The reason for these disparities might lie in the complex relationship between age, financial independence, and ethnicity. Many smokers start at an early age, before employment can be a factor, while many become addicted due to job stress and find it hard to quit after unemployment. Conversely, a systematic review of the Iranian population showed that hookah use was more common among unemployed individuals, socialization and cost-effectiveness being driving factors (47). In conclusion, our results align with some past studies on employment status and cigarette and hookah smoking status.

### *Relationship Between Educational Attainment and Smoking Status*

The prevalence of cigarette smoking was almost evenly distributed among various educational categories, while hookah use was mostly seen at lower educational levels. Pervious publications have shown that smoking cessation is associated to higher education in the general adult population, with these disparities being linked to earlier disadvantageous statuses (48-50). Hookah use within the Iranian population has also been documented to have an inverse correlation with education levels (51). Although no significant disparity existed within the education level of cigarette smokers, in contrast to past studies, the propensity of individuals with lower education to use hookah was well documented within this study.

## Electrocardiogram Interpretation

### *Cigarettes and Minor Abnormalities*

Our results showed that minor ECG abnormalities were significantly more prevalent among cigarette smokers. Significant findings included: 1) ST-segment elevation, 2) Left axis deviation (LAD), 3) Sinus bradycardia, and 4) High amplitude P-waves. Of these only bradycardia and high amplitude P-waves remained significant in the revised model. While ST segment elevations can be an incidental finding in some individuals, their occurrence in smokers may indicate underlying ischemic changes (52). Study in mice have shown the impairment of endothelial relaxation resulting from reduced Nitric Oxide levels when exposed to nicotine. Additionally, continuous vascular injury in chronic exposure to cigarette smoke has been documented to arise from oxidative stress and increased pro-inflammatory cytokines, such as interleukin 6, interleukin 1β, and tumor necrosis factor α (TNF-α). In vitro studies show that cigarette smoke increases the release of pro-atherogenic cytokines (Interleukins 6 & 8) and increases the expression of adhesion molecules on endothelial surfaces (53-55). Endothelial cell death and damage have also been seen as a direct result of cigarette smoke (56). Cigarette smokers are also thought to have increased odds of dyslipidemia and insulin resistance which further drive atherosclerosis (41). These vascular insults result in a chronic reduction of myocardial blood supply, caused by coronary vasospasm and accelerated atherosclerosis, resulting in CAD and contributing to chronic changes in the ST segment (57). In the study population, an insignificant increased prevalence of LAD was noted among cigarette smokers compared to non-smokers. Although not corroborated in this study, cigarette smokers tend to have higher LV mass index and thickness, with the increased prevalence of LVH and resulting LAD being due to structural alteration from the previously described pathways in addition to elevated systemic arterial pressure (41, 58-60). Pervious publications have documented the hyper-activation of the sympathetic nervous system caused by nicotine exposure and its resulting increase in heart rate, with habitual users having an increased sympathetic drive at rest (61). Our results showed the opposite in this population, as cigarette smokers had significantly increased odds of sinus bradycardia compared to non-smokers. Chronic cigarette use has been documented

to lead to autonomic imbalance, although this typically manifests as decreased vagal tone as opposed to an increase (62). However, cases of increased parasympathetic stimulation in response to nicotine have been documented, with these cases typically secondary to extremely high doses and intoxication, causing ganglionic blockade and bradycardia (63). Regarding high amplitude P-waves, chronic cigarette smokers have been documented to have higher than average pulmonary arterial pressure, as a result of sustained hypoxia and chronic obstructive pulmonary disease (COPD). The development of pulmonary arterial hypertension (PAH) results in right atrial remodeling and enlargement (RAE), which could account for these findings (64, 65). The persistence of sinus bradycardia and high amplitude P-waves in the revised model suggests that these changes are more directly correlated with chronic smoking rather than other confounding factors like sex or age. These findings indicate prolonged effects of smoking on both autonomic regulation and structural changes in the heart and introduce multiple pathophysiological mechanisms.

### *Hookah and Minor Abnormalities*

The only significant minor abnormality found among hookah users was sinus tachycardia, which did not remain significant in the adjusted model, along with all other borderline findings. Few studies have analyzed the short- and long-term cardiovascular consequences of hookah use. Our findings revealed that, although not statistically significant, hookah users had lower odds of presenting with sinus tachycardia than non-smokers. However, this did not translate to a significantly higher prevalence of sinus bradycardia. As previously stated, chronic exposure to nicotine and tobacco is associated with greater odds of sinus tachycardia. However, similar to the cigarette smokers group, this association was not seen within our study (61). One key difference between cigarette and hookah smokers is the plasma concentration of nicotine seen throughout a session. Hookah users tend to have significantly lower concentrations of nicotine early on, which drastically increases as they continue to smoke (66). Moreover, hookah users have greater expired CO levels and blood carboxyhemoglobin (COHb) values compared with cigarette smokers (67). The sociocultural context of hookah smoking, typically performed in relaxed settings, as opposed to the often-stressful environments associated with cigarette smoking, could modulate physiological stress responses. This environmental context may influence autonomic tone, favoring parasympathetic dominance and hence a reduction in incidences of sinus tachycardia (68). In conclusion, our study failed to demonstrate any significant difference in the baseline heart rate of hookah users compared to non-smokers, unlike the significant bradycardia seen in cigarette smokers. This lack of difference is possibly due to the diverse interplay of various factors and key differences seen in hookah smokers compared to cigarette smokers.

### *Cigarettes, Hookah and Major ECG Abnormalities*

Significant major findings included isolated ST-T and LVH plus ST-T abnormalities, with the Brugada pattern being borderline amongst cigarette smokers. None of these findings remained significant in the adjusted model. As previously stated, cigarette smoking was associated with various cardiovascular risk factors, including atherosclerosis, endothelial dysfunction, and increased oxidative stress (41, 42, 53-56). The combination of these factors leads to CAD, and underlying ischemic changes may cause changes in the ST-T segment. Additionally, smokers tend to have a greater prevalence of LVH than the average adult population, typically as a result of HTN. Among hypertensive patients, non-specific repolarization disorders represent the most common abnormalities found in ECGs (69). Frequently, LVH is associated with ST-segment changes including ST depression, termed as a “strain pattern”, however, LVH and HCM are also commonly correlated with ST-segment elevation, particularly in leads V2-3 (70, 71). Similar to that of ST segment changes, LVH is also associated with abnormalities in the T-wave, most commonly manifesting as T-wave inversion (TWI) (72). Moreover, cigarette smokers have been documented to have truncated ST and QT

segments in comparison with non-smokers (73). Acute reversible changes in ST-T have also been seen during cigarette smoking (74). The Brugada pattern is characterized by specific ECG findings that may indicate an increased risk of sudden cardiac death because of ventricular arrhythmias. Although a borderline Brugada pattern in smokers may initially appear significant, its disappearance in adjusted models suggests that smoking alone may not be a direct cause. Few studies have been done on the correlation between cigarette smoking and Brugada, with one case report highlighting its acute onset and spontaneous resolution associated with nicotine toxicity (75). In conclusion, the underlying mechanisms linking cigarette smoking to the observed major ECG alterations seem to be multifactorial, with chronic nicotine use manifesting as isolated ST-T changes, LVH with ST-T abnormalities, and possibly even occasionally mimic patterns like Brugada syndrome in our study population. Major ECG abnormalities were, albeit insignificantly, more prevalent in hookah users than cigarette smokers. Amongst these, only LVH plus ST-T abnormalities were found to be significant, with isolated ST-T abnormalities being documented as borderline. Similar to that of cigarette smokers, none of these findings were corroborated in the adjusted model. AS previously described, hookah and cigarette smoking carry key differences, which account for the subtle statistical disparities found between the two groups (66-68). While the specific pathways are complex and multifactorial, many of the mechanisms described for cigarette smokers provide a coherent explanation for the prevalence and characteristics of ECG changes seen in hookah users.

### Strengths and limitations

One of the strengths of this study is the large sample size from the MASHAD cohort, which enhances statistical power and generalizability. The use of standardized MC ensures reliable ECG classification, and adjustments for key confounders minimize bias, although we could not consider all the confounders due to the limited frequency of ECG changesSeparate analyses of cigarette and hookah smoking provide novel insights into their cardiovascular effects. However, the cross-sectional design limits causal inference, and reliance on self-reported smoking habits may introduce recall bias. The lack of biochemical validation and long-term follow-up further restrict exposure accuracy and assessment of ECG changes over time. Despite these limitations, this study contributes valuable evidence on smoking-related cardiovascular risks.

## Conclusion

In conclusion, our study found several statistically significant ECG abnormalities in cigarette and hookah smokers compared to a similar non-smoker population. Some of these findings, although only minor, remained significant in the adjusted model for sex, age, education, and employment. Interestingly, some of these findings contradicted with those of previous publications, especially regarding sinus bradycardia in cigarette smokers. In this cohort, we documented major and minor ECG findings in cigarette and hookah smokers, compared their significance, and discussed possible underlying mechanisms for hese differences.

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### Ethics Approval and Consent of Participant

The Ethics Committee of Mashhad University of Medical Sciences (MUMS) approved the study (IR.MUMS.MEDICAL.REC.1399.783). The study was confirmed to meet the ethical principles of the Helsinki Agreement in medical research.

### Availability of Data and Materials

The data is the property of MUMS and can be made available upon a reasonable request through the corresponding author.

### Competing Interests

The authors declare that there are no conflicts of interest.

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