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REVIEW

The Association Between Smoking Behavior and the Risk of Hypertension: Review of the Observational and Genetic Evidence

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Background: Cigarette smoking is one of the world's largest avoidable risk factors for morbidity and mortality. Numerous studies have investigated the association between smoking and hypertension (HTN). Although observational data and cross-sectional research often exhibit a link between smoking and HTN, establishing causation remains challenging owing to potential confounding variables. Mendelian randomization (MR), a genetic epidemiological technique that employs genetic variants as instrumental variables, offers a more robust approach for evaluating causal links. This review aimed to explore both the observational and causal relationships between smoking and the risk of HTN.

Methodology: A comprehensive literature search across major electronic databases was conducted to identify relevant observational and Mendelian randomization (MR) studies on smoking and HTN risk. Various characteristics were included during study selection, such as study design, exposure assessment, and age range. Standardized processes were used for data retrieval and quality evaluation.

Results: Analysis of observational data revealed a paradoxical association between smoking and the risk of HTN, where a lower risk was observed among current smokers when compared to non-smokers. However, observational analysis also presented a dose-response effect with greater smoking intensity showed a modest linear increase in HTN risk, and older smoking initiation was associated with a slight increase in HTN risk (compared with younger). In contrast, MR-based causal estimates provide inconsistent evidence regarding the causal relationship between smoking behavior and HTN. Some MR analyses indicated a potential causal link between smoking and HTN; but this was not consistent.

Conclusion: Observational studies suggest a paradoxical association between smoking and HTN. However, MR studies do not provide sufficient evidence to establish a causal relationship. Regardless, lifestyle variables remain crucial for overall health. Healthcare professionals should regularly assess smoking status and provide counseling for quitting. Further research is needed to clarify the underlying processes, identify mediators, and evaluate the interventions.

Keywords: smoking behavior, high blood pressure, hypertension, Mendelian randomization

Introduction

Background and Significance

Hypertension (HTN) is a widespread disorder, and its prevalence has increased significantly over the past decades.[1] HTN is a silent, yet frequently disregarded threat to global health. It serves as a primary risk contributor to cardiovascular diseases (CVDs), including heart attacks, strokes, and heart failure, affecting over one billion individuals globally. Notably, almost 10 million deaths worldwide have been reported to be a consequence of HTN. The identification of risk factors is paramount for addressing this global health catastrophe.[2]

Smoking itself has emerged as the most ignored cause of death globally. Extensive research has linked smoking to increased inflammation, dysfunction of endothelial cells lining the blood vessels, and alterations in HTN regulation, collectively contributing to an elevated risk of hypertension.[3] The pervasive habit of smoking is injurious to cardiovascular health and is associated with respiratory conditions such as lung cancer and asthma. More than 7 million people succumb to smoking-related

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causes annually, with a projected increase to 10 million by 2030. From 1990 to 2019, Saudi Arabia experienced a 39% increase in male smoking prevalence and a 45% increase in female smoking rates, with a smoking prevalence of 14.36% in 2019 adjusted for gender and age.[4] HTN is a growing global health concern, particularly in Middle East countries.[5] It is estimated to be 29.5%, with variability across countries. In Saudi Arabia, HTN was the leading risk factor for most deaths.[6] The Coronary Artery Disease in Saudis Study reported a 26.1% prevalence, with higher rates in men (28.6%) than women aged 30 to 70 years.[7]

Healthcare experts and concerned agencies emphasize the need to understand the causes behind the smoking's consequences, smoker behaviors, and effective strategies to address this pressing public health concern.[8,9]

The existing literature on the relationship between cigarette smoking and HTN is insufficient to draw definitive conclusions. While some studies have suggested a positive association between smoking and increased BP, others have reported no clear relationship between smoking and HTN.[10–12] Carefully planned studies in healthy human participants have indicated a direct association between smoking uptake and a sudden increase in BP.[13] In most of these investigations, nonsmoking subjects were exposed to regulated levels of cigarette smoke, and their blood pressure was recorded prior to, during, and following exposure. The results regularly showed a brief increase in blood pressure after smoking, indicating that smoking may have an immediate negative effect on the cardiovascular system. The inconsistency in findings can be ascribed to various factors, including variations in the study design, cohort characteristics, and exposure assessment techniques. Moreover, robust evidence from controlled studies underscores that quitting smoking significantly affects BP regulation, heartbeat, and plasma concentrations of norepinephrine and adrenaline in smokers.[14] However, the epidemiological landscape reveals a complex relationship between tobacco use and HTN, with some population-based studies demonstrating a link between smoking and hypertension.[15–17] Conversely, certain studies failed to provide supporting data and, in some instances, even showed a negative correlation.[18,19]

Smoking may contribute to high blood pressure (HTN) through various biological pathways. Oxidative stress from cigarette smoke can damage cells and tissues, impairing the endothelium, the inner lining of blood vessels. This can lead to blood vessel constriction and increased peripheral resistance, contributing to HTN. Additionally, nicotine's effect on the sympathetic nervous system can activate the fight-or-flight response, increasing heart rate, blood vessel constriction, and blood pressure.[20]

The correlation between smoking and the risk of HTN has been the focus of numerous investigations; however, it remains controversial because of the inherent limitations of observational, cross-sectional studies, which are susceptible to confounding factors. To date, the causal relationship between smoking and HTN has not been conclusively demonstrated.

Recognizing the intricate association between smoking behavior and HTN is imperative for global health, particularly given the latter's status as a major risk factor for the development of CVDs. Hypertension affects over 1.0 billion adults worldwide, and smoking contributes to approximately 7.0 million deaths annually.[9] Consequently, understanding the correlation between these two conditions is crucial for developing effective management strategies and enhancing cardiovascular health in general.

Mendelian randomization (MR), a genetic epidemiological technique, has emerged as a valuable tool for shedding light on the potential causal interactions between smoking and other health-related outcomes. MR leverages existing genetic variables that are reliably associated with smoking behaviors (or any traits) to better estimate the 'causal' effect of exposure on outcomes. This review specifically explored the link between tobacco smoking and HTN risk using the MR approach.

Objectives of the Research

The present review aimed to: (i) assess the observational relationship between smoking and the risk of HTN through a critical examination of existing observational studies, and (ii) discern any potential causal relationship between smoking and HTN by examining the available Mendelian randomization (MR) studies.

Methods

Literature Search Strategy

To identify pertinent studies on the relationship between smoking and hypertension, a comprehensive narrative review was conducted across major electronic databases, including Google Scholar, PubMed, EMBASE, and the Cochrane

Library. The review used keywords such as "smoking behavior", "high blood pressure" or "hypertension", and "smoking" or "tobacco use", tobacco use, along with associated terms. Other search terms, such as observational studies and MR investigations, were incorporated to focus on the specific study designs. Only studies published in English between 2000 and 2023 were included. A second reviewer used the same search terms and criteria to independently search the relevant materials. After comparing their findings, the two reviewers decided which papers should be included in the review.

Study Selection Criteria

Studies included in this narrative review were conducted using specific criteria. Observational studies (cohort, cross-sectional) and MR studies focusing on individuals aged ≥ 18 years with exposure to smoking were considered. Validating and generalizing MR findings can be accomplished by comparing outcomes with data from longitudinal cohort studies. The case of causation is strengthened if MR and longitudinal cohort studies consistently reveal comparable correlations between exposure and outcomes. However, disparities in study populations, techniques of measurement, or underlying causal mechanisms may be the cause of any discrepancy between the two types of studies. Reviews, case reports, editorials, letters to editors, and studies involving non-human subjects were excluded from this narrative review.

Data Extraction and Quality Assessment

Following the shortlisting of eligible studies, data were procured through a standardized data extraction procedure. The extracted data encompassed information pertaining to the study design, objectives, population, Methods of outcome assessment, key findings, and identified limitations. The quality of each study was assessed based on predefined criteria, including the robustness of the study design, characteristics of the study population, accuracy of exposure measurements, and appropriateness of statistical methods for outcome assessment.

Several measures have been implemented to mitigate potential confounding factors and bias in the analysis of observational studies. These steps involved stratification by relevant characteristics such as age range, sex, socio-economic status, ethnicity, and body mass index (BMI) in the analysis of observational studies. Adjustments for significant variables were made in the statistical analyses to enhance the robustness of the findings.

To derive causal insights into the relationship between smoking and HTN, certain MR studies were examined and compared with the outcomes of the observational studies incorporated in this review.

Observational Studies Investigating the Smoking-Hypertension Association

Study Characteristics

Numerous observational studies have explored the relationship between smoking habits and the risk of HTN. The findings of these studies yielded inconsistent findings. Some studies such as research conducted on Vietnamese men[12] revealed a dose-response association between the duration and intensity of smoking and the risk of HTN. Additionally, Gao et al[21] found that heavy machine-rolled cigarette smokers had a significantly elevated risk of HTN.

However, not all studies have established a significant correlation between smoking and HTN. According to Diana et al[22] HTN is highly prevalent in middle-aged men and is associated with smoking and physical activity. Conversely, Alomari and Al-Sheyab[10] found an inverse association between smoking and HTN risk in male teenagers smokers, suggesting lower cardiovascular risk measurements. However, this finding contradicts the established negative health effects of smoking on cardiovascular health.

Moreover, Liu and Byrd[23] suggested that existing smokers had a lower risk of HTN than nonsmokers. However, the correlation between BP and smoking status has not yet been definitively established, as reported by Abtahi et al[24]. Some evidence suggests that smoking and HTN may be linked in a dose-dependent manner despite inconsistent results. This suggests that heavier smokers may be more likely to develop HTN than lighter smokers. This implies that smoking may be a causative factor in the development of HTN, although further investigation is required to verify this. The key findings of observational studies regarding the association between smoking and the risk of HTN are provided in Table 1.

Table 1 Findings of the Review Sources

Study design and Authors	Study Purpose	Study Sample	Key Findings	Limitations	Conclusion
Cross sectional study, Thy et al[8]	To examine the relation between smoking and HTN in a population-built sample of Vietnamese men.	All the study partakers were 25 to 64 years men (n = 910).	-A significant trend was observed in increasing incidence of HTN with growing years (P= 0.05). -People with a smoking history of 30 years or more and those who had smoked 20 pack-years or more showed a 1.52-fold (95% CI: 0.95–2.44) and 1.34-fold (95% CI: 0.94–1.91) increase in HTN's risk, respectively, compared to non-smokers. -While current smokers (prevalence ratio U 1.08, 95% CI 0.70–1.68) were not statistically more likely to have HTN than never-smokers, they were more likely to have it than ex-smokers.	-It was not possible to calculate the ex-smokers' pack-years of smoking or the amount of tobacco they used. -There was no objective way to measure sodium in food. -It is problematic to measure salt intake using a questionnaire. The results of this study might have been impacted if an appropriate assessment of sodium intake had not been considered	The intensity and duration of smoking both raised the risk of HTN, but existing smokers did not have a greater risk than never-smokers.
Cross sectional study, Liu and Byrd et al[18]	To investigate the connection between smoking and high blood pressure in patients	n = 7829, who were 18 years of age regardless of gender.	-Current smokers and former smokers had lower DBP than non-smokers by 1.3 mmHg (95% CI: −2.8, −0.2, P=0.02) and 0.9 mmHg (95% CI: −1.7, −0.03, P=0.04), respectively, among HTN patients. -Compared to non-smokers, current smokers had a 22% lower risk of uncontrolled blood pressure (OR = 0.78, 95% CI: 0.64, 0.94, P>0.01).	-Many confounding factors, like nutrition, lipid profile, physical activity, and medical history of diseases, may have played a key part in this link. -Self-reported smoking status, the length of HTN, antihypertensive medication use, and dosages were not collected, which could have led to measurement bias in the study.	Among the study individuals, a negative correlation was seen between subtypes of uncontrolled BP and cigarette smoking.
Cross sectional study, Abtahi et al[19]	To examine correlation between cigarette smoking and BP among teachers residing in Shiraz, Iran	n=3115 teachers. Out of which 1842 (59%) were female teachers.	-The smoking prevalence was 5.85%, although pre-HTN and HTN rates were 42.6% and 18.2%, respectively. Men and the elderly were more likely to have HTN, but smokers were more likely to have pre-HTN. -Although the difference was not statistically significant, the study discovered that heavy smokers had a wider mean range of systolic and diastolic HTN as well as pulse pressure than did people who smoked fewer than 20 packs annually.	-The study did not control other potential confounding factors, such as diet, exercise, and genetics. -The sample size is not enough to clearly correlate the two variables.	-BP and smoking status do not yet clearly correlate. But it appears that cutting back on smoking, or at least quitting altogether, would dramatically lower BP.

Cross sectional study[6]	To investigate the association between smoking and HTN	n=244 healthy teenagers from both genders	-In comparison to non-smokers, the smokers were younger (P=0.001), lighter (P=0.001), and shorter (P=0.001), according to the data. −20.6% of the variations in SBP were explained by the smoker's status (R2=0.206, F =46, P<0.003). -In smokers, the mean SBP was 108.8, while the mean DBP was 55.4 (P<0.02). -When comparing current smokers to non-smokers, both SBP and DBP were lower (P<0.05). -Low BP was found common among smoker's students.	-The study was cross-sectional and included adequate survey data, but it lacked temporal or causal analysis. -The self-reported smoking status is inconsistent, especially in this age group, and the sample size was small. -In a cross-sectional investigation, confounding variables and reverse causality are nearly inevitable	Adolescent cigarette smoking appears to lower CVD measurements. An inverse relation was found between two variables.
Cross sectional study Diana et al[17]	To examine the relation between smoking, physical activity and HTN among middle-aged people.	n=112, based on middle aged men (45–59 years old).	-The study showed a high incidence of HTN in middle-aged men. -The chi square test revealed a significant (p=0.039) correlation between blood pressure and smoking habit. -Compared to non-smokers, a greater percentage of smokers had normal blood pressure, prehypertension, and hypertension stage 1. In the meantime, stage 2 hypertension is more common in non-smokers.	-The fact that there were only 112 participants in the study may have limited how broadly the results can be applied. -Because the information on physical activity and smoking habits was self-reported, bias may have crept in. -The study's sole method of measuring physical activity was 24-hour physical activity recall, which could not be a reliable indicator of participants' typical levels of physical activity.	HTN was extremely common in middle-aged males and that it was correlated with both physical activity and smoking
Cohort study, Gao et al[16]	To evaluate the epidemiological verification of a potential link between smoking and the likelihood of developing HTN in the future.	n= 5625 (2563 males and 3062 females).	-Compared to non-smokers, heavy machine-rolled cigarette smokers had a higher risk of hypertension (HR: 1.50, 95% CI: 1.05–2.16). -The risk of developing HTN in the future was elevated by the combination of excessive drinking and smoking, with an altered HR of 2.58 (95% CI: 1.06–6.33).	-There was insufficient information available on the length of exposure because the data on tobacco intake came solely from the baseline survey. -The interview survey was used to gather information about smoking, and laboratory testing was not used to confirm the individuals' real smoking status, which could have resulted in misleading data. -The documented period of the development of HTN may be erroneous because of the lengthy survey intervals and insufficient time for follow-up visits.	When compared to non-smokers, heavy machine-rolled cigarette smokers had a statistically significant higher risk of HTN.

Strengths and Limitations of Observational Studies

In observational studies, subjects were observed and documented without intervention. By gathering data from individuals in their natural environment, they can provide accurate and realistic data on the impacts of exposure, which gives them various advantages over other study designs. These advantages include generalizability and cost-effectiveness.[25] Likewise, observational studies have the capacity to uncover novel risk factors for disease, which can guide future research in randomized controlled trials (RCTs).[26]

Although observational studies have advantages, they have significant drawbacks that may impact the interpretation of the results. For example, if study participants are not representative of the population being studied, a selection bias may arise.[27] This may cause the genuine association between smoking and hypertension to be overestimated or underestimated.[28] Information bias can also impact observational studies, leading to inaccurate assessment of the relationship between smoking and HTN due to inaccurate measures of exposure or outcome factors.[29]

In addition, research based on observational data cannot prove causation, making it impossible to show a direct connection between smoking and hypertension. This restriction results from the fact that observational studies do not have the control that experimental designs provide, which makes it difficult to exclude the possibility that other factors, such as nutrition, exercise, or genetics, may have an impact on the association that was observed.[27] Therefore, it is crucial to interpret the findings of observational studies by considering potential biases and competing theories to explain observed connections. The authors emphasize that, to support causal inferences, MR investigations may be combined with other observational study designs, such as cohort and longitudinal studies. They also touch on the significance of considering alternative explanations to account for correlations between exposures and observed results.[30]

Introduction to Mendelian Randomization (MR)

Concept and Principles

MR is an important technique employed to explore the potential causal associations between exposure and outcomes. Naturally occurring variation in an individual's genetic code is denoted as a genetic variant.[31] Single nucleotide polymorphisms (SNPs) have emerged as the most frequently utilized genetic variants in MR analysis. Because of the random inheritance of SNPs from parents to offspring, they are instrumental in MR analysis and unaffected by variables such as nutrition, exercise, or lifestyle. This characteristic allows researchers to examine the causal relationship between exposure and outcome by employing SNPs as proxies for exposure.[32]

The fundamental concept underlying Mendelian randomization is that if a genetic variant causes a change in exposure (such as drinking or smoking) and this change is causally linked to a disease, then the genetic variant should also be associated with the risk of the disease.[33] Capitalizing on the random assignment of genetic variants during meiosis enhances resistance to confounding in MR analysis compared with traditional observational epidemiological studies.[34] Additionally, reverse causation is circumvented in MR-based analyses because the genotype remains unaffected by the disease.[32]

The validity of MR studies rests on specific core assumptions (Figure 1)

1. Genetic variations must be associated with the relevant exposure under investigation to ensure that the genetic variants accurately represent the exposure.
2. Genetic variations should solely influence the outcome by exposing the relevant area of interest, eliminating the possibility of pleiotropic effects, where the genetic mutation affects the outcome in various ways.
3. Genetic variations should not be linked to factors that skew the association between exposure and outcome, guarding against the impact of unmeasured factors.

Adhering to these assumptions, MR provides a robust and powerful tool for inferring causal relationships between exposures and outcomes and has been successfully applied to investigate a diverse range of exposures, including environmental toxins, dietary factors, and behavioral patterns.[36]

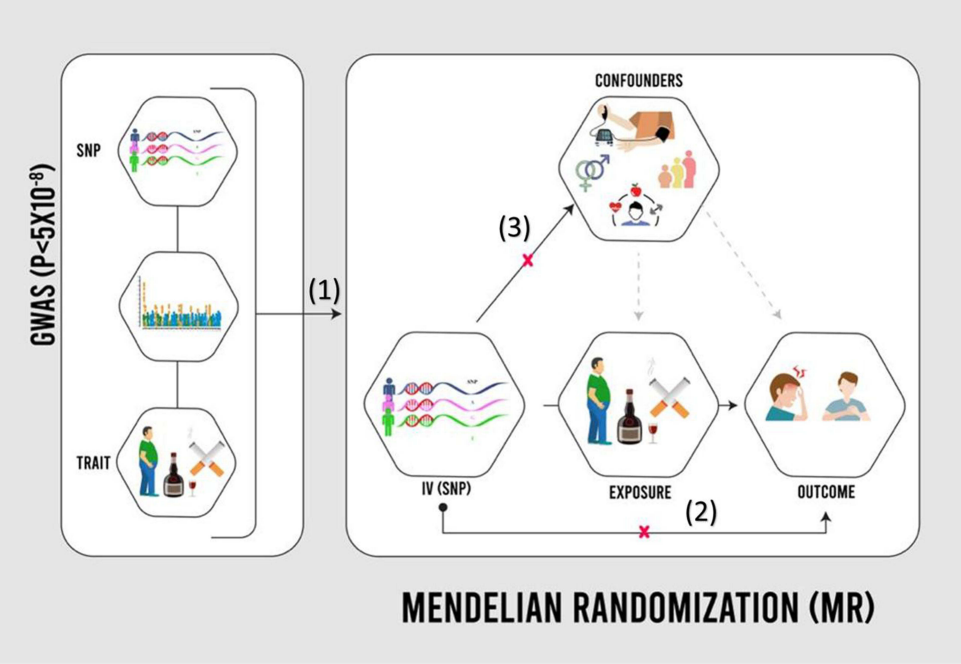

Figure 1 Mendelian Randomization (MR) Design. Reprinted from Jareebi MA, Alqassim AY. The impact of educational attainment on mental health: A Causal Assessment from the UKB and FinnGen Cohorts. *Medicine*. 2024;103(26):e38602. Creative Commons.[35]

Strength and Limitations of Mendelian Randomization (MR)

MR is a robust epidemiological technique that employs genetic variations as instrumental tools to assess causal relationships between exposures, such as smoking, and outcomes, such as HTN. Its strength lies in the utilization of genetic variations randomly assigned at conception, mimicking natural RCTs. This approach minimizes biases from reverse causality and confounding, which are commonly observed in observational studies. Through MR, researchers can calculate the causal effects of modifiable exposures on health outcomes, offering crucial insights for treatment strategies and policy decisions aimed at mitigating the adverse effects of these exposures.[37]

Despite its strengths, MR studies have limitations, and bias or misleading connections may occur if key assumptions, such as relevance, independence, and exclusion restrictions, are violated.[38] Pleiotropy, a concern in which a single genetic variant influences multiple biological pathways, complicates the identification of the specific pathway driving the observed connection, making the interpretation of MR results more challenging. Achieving sufficient statistical power in MR studies typically requires large sample sizes and relies on the availability of reliable genetic instruments highly correlated with exposure but uncorrelated with confounders or pleiotropic effects.[31]

Two statistical techniques frequently employed in MR analyses are the Two-sample Mendelian Randomization (2SMR) and Inverse Variance-Weighted (IVW) regression. When summary-level data from Genome-Wide Association Studies (GWAS) are accessible for both the exposure and outcome of interest, 2SMR is a popular method. IVW regression, another prevalent technique, employs the genetic variant as an instrumental variable (IV) in a regression-based approach to estimate the causal impact of exposure on the outcome.[39]

Readers seeking a solid foundation and understanding the principles and applications of MR can refer to useful resources.[36,40,41] MR-base, a database and analytical platform for MR developed by the MRC Integrative Epidemiology Unit at the University of Bristol, is a valuable resource (www.mrbase.org).

Mendelian Randomization Studies on Smoking and Hypertension

Genetic Variants Associated with Smoking Behavior

Mendelian randomization (MR) is a method that uses genetic variations as a proxy for exposure to smoking. These variations are inherited at conception and remain unaffected by a person's lifestyle or environment. Researchers identify genetic variations strongly linked to smoking behavior, assume random assignment at birth, and examine how these

genetic variations affect the risk of hypertension. MR is powerful because it helps control confounding factors in observational studies. If genetic variations linked to smoking predict hypertension risk, it strengthens the evidence that smoking causally influences hypertension. However, MR is not foolproof, as the chosen genetic variations must reflect smoking behavior and not have independent effects on blood pressure. Additionally, MR studies may not capture the full complexity of how smoking affects health. Genetic variants associated with smoking behavior have been investigated and scrutinized through (GWAS) and (MR) analyses. The objective was to understand smoking behavior and elucidate the causal relationships between these genetic variations and prospective outcomes.[42] The central variable in this review, smoking, represents one of the numerous genetic variations linked to the characteristics of interest that GWAS has unveiled. Several genetic variants have been identified as putative Instrumental Variables (IVs) for smoking behavior, nicotine dependence, and regular cigarette consumption. The two MR studies included in this review used variants within the CHRNA5/CHRNA3/CHRNB4 gene cluster as their IVs. These genes encode the nicotinic acetylcholine receptor, a fundamental target of nicotine in the CNS. The most extensively researched genetic variants associated with smoking behavior are as follows:

a. CHRNA5/CHRNA3/CHRNB4: These genes encode the primary targets of nicotine in the brain and the nicotinic acetylcholine receptor (nAChR). Variants in these genes have been correlated with a higher smoking intensity and an increased risk of smoking initiation.[43]
b. CYP2A6: Responsible for producing the enzyme required to metabolize nicotine; variants in the CYP2A6 gene influence nicotine metabolism and have been linked to the success of smoking cessation.[44]
c. DRD2: Encoding the dopamine D2 receptor, a crucial component of the brain's reward system, DRD2 has been associated with a higher risk of initiating smoking and developing nicotine addiction.[45]
d. HTR2A: The HTR2A gene encodes the serotonin 2A receptor, another vital element in the incentive system. Genetic variations in HTR2A have been linked to an increased likelihood of developing nicotine addiction and initiating smoking.[46]
e. MAOA: Encoding an enzyme that breaks down dopamine and other neurotransmitters. Variations in MAOA have been associated with a higher likelihood of initiating smoking and developing nicotine addiction.[46]

Genetic Variants as Instrumental Variables

Genetic variants serve as instrumental variables (IVs) in MR analysis, playing a pivotal role in characterizing relevant risk factors and investigating the causal relationship between exposure and outcome. IVs act as exposure proxies, mitigating potential confounding variables inherent in typical observational studies and thereby enabling researchers to draw causal inferences.[41,47] The utilization of genetic variants as proxies for smoking exposure helps researchers circumvent the issues associated with observational studies. As these genetic variations are inherited at conception and remain unaffected by smoking or other confounding factors, they are considered excellent candidates for IVs. Researchers can infer a potential causal relationship between smoking and hypertension by employing genetic variants as IVs in MR analyses.[31]

The initial crucial step in MR analysis involves the careful selection of IVs. Genetic variants must meet specific criteria to be considered as sensible IVs. These criteria include:

i. **Relevance**: Genetic variation needs to be associated with relevant exposure, in this case, smoking behavior.
ii. **Independence**: The genetic variant must not be linked to variables that could influence the connection between exposure and outcome, thus potentially biasing the results.
iii. **Exclusion Restriction**: The Exposure (smoking) should be the only way in which the genetic variant influences the outcome (risk of hypertension).

Researchers have conducted GWAS to assess the relationship between genetic variations across the genome and smoking initiation, intensity, or cessation, aiming to identify potential IVs for smoking behavior. Variants with significant

relationships undergo assessment for relevance, independence, and exclusion restriction using various statistical techniques (as mentioned above) and the current biological understanding.[31]

Summary of Findings

Two MR studies explored the association between smoking and the risk of hypertension.[48,49] These investigations revealed that smoking is a causative risk factor for increased resting heart rate and decreased systolic and diastolic blood pressures. However, there is limited evidence connecting smoking directly to HTN, and neither study was able to establish a conclusive causal relationship between smoking and HTN. Two-sample Mendelian Randomization (2SMR), a statistical approach used to estimate the causal impact of smoking behavior on hypertension, was employed in both studies.

In the 2SMR, the relationships between each genetic variant and both smoking behavior and HTN were compared across different GWAS datasets. The study results included confidence intervals, indicating the level of uncertainty in the estimated causal effect. For instance, the first study found that systolic blood pressure decreases by 0.22 mm Hg (95% confidence interval, −0.32 to −0.12 mm Hg) for every additional pack-year of smoking. This implies that the actual causative effect may fall outside the range of −0.32 mm Hg to −0.12 mm Hg, but it is most likely within this range. A detailed summary of these findings is presented in Table 2.

Implications and Interpretations

The MR studies consistently provided evidence of the association between smoking behavior and HTN. These investigations revealed that smoking is a risk factor for increased resting heart rate and lower systolic and diastolic BP. These findings align with those of observational research, which also indicates a correlation between smoking and cardiovascular outcomes. However, MR research has not established a significant correlation between smoking habits and the risk of hypertension. This contrasts with certain observational study findings that suggest smoking increases the risk of HTN.

Several potential reasons may account for the observed discrepancy between MR studies and observational studies. One possibility is that the genetic variations utilized in MR research may not serve as reliable proxies for smoking behavior. It is plausible that smoking influences hypertension via a mechanism different from that mediated by genetic variations employed in MR investigations.

Compared to the results of observational research, MR findings provide stronger evidence of a causal association between smoking behavior and reduced systolic and diastolic blood pressure, as well as a higher resting heart rate. This is attributed to the reduced susceptibility of MR investigations to confounding bias compared with observational research. Nevertheless, MR research does not offer conclusive validation of the causal relationship between smoking behavior and HTN.

Comparison of Observational and MR Studies

Both observational and MR studies serve as complementary approaches to explore the causal links between exposure and outcomes. Observational studies, owing to their substantial sample sizes and real-world contexts, offer valuable insights into the relationship between smoking and the risk of HTN. However, they also have unique advantages and disadvantages. The purpose of this narrative review was to evaluate and contrast the two methods and discuss how they might affect our comprehension of the cause-and-effect link between smoking and HTN. ”Several genetic variants have been identified as putative Instrumental Variables (IVs) for smoking behavior, nicotine dependence, and regular cigarette consumption. The key differences between the observational and MR studies are shown in Table 3.

Consistency of Findings

Observational studies, including cohort and cross-sectional studies, have frequently indicated a connection between smoking and HTN. Significant research suggests that smokers are more prone to acquiring HTN than non-smokers, with the risk increasing by 30–40%.[50] However, some studies report no significant relationship between smoking and hypertension, and some investigations even suggest an inverse relationship.[10,23,24] Similarly, MR studies are unable to

Table 2 Summary of the MR Studies

Study design and Authors	Study Purpose	Study Sample	Exposure & Outcomes	Key Findings	Limitations	Conclusion
MR, Åsvold **et al**[36]	To examine the casual relation of the rs1051730 T allele with CVDs risk factors such as HTN.	All the adults aged 20 years or above n=56,625	-Genetic variant (rs1051730 T) allele as a measure of smoking exposure. -CVDs risk factors including BMI, HTN, HDL & glucose.	-An extra rs1051730 allele was associated with 0.27 mmHg (95% CI: 0.04, 0.49), lower SBP (P-value <0.02), but no association with DBP was detected. -For every extra rs1051730 T allele, there was a 0.34% (95% CI: 0.02, 0.66) increase in HDL concentration in the whole study group; however, this difference did not occur in smoking subtypes, such as current smokers (0.37%, P=0.2). -The rs1051730 T allele was linked to a reduced triglyceride concentration of 1.16% (95% CI: 0.03, 2.28) in current smokers. This effect was mitigated after adjusting for BMI (0.03%, P = 0.96). -Among current smokers, there was no discernible correlation seen between rs1051730 and either total cholesterol or glucose levels.	-This study only contained one SNP, and as single SNPs are typically weak instruments, a polygenic score—which raises both the IV estimate's precision and statistical power—would be more reliable. -They claimed that in addition to smoking, there may have been other ways for rs1051730 to have affected the result, which would go against one of the IV assumptions (positive relationship between rs1051730 and BMI).	The results showed that blood pressure, serum lipid levels, and glucose levels were not significantly influenced by smoking.

MR, Linneberg A **e al.**[37]	To examine the correlations of smoking level and smoking intensity with systolic and diastolic BP, HTN, and resting heart rate.	All the individuals aged 18 years or above n=141,317	-A genetic variant rs16969968 or rs1051730 was used as a measure for smoking intensity in current smokers. -Hypertension	-In observational studies among present smokers, upsurge level of smoking intensity was linked with higher resting heartbeat rate (0.21 bpm; 95% confidence interval 0.19; 0.24), and somewhat higher diastolic BP (0.05 mm Hg; 95% confidence interval 0.02; 0.08) and systolic BP (0.08 mm Hg; 95% confidence interval 0.03; 0.13). -In MR studies among current smokers each smoking-related allele of rs16969968 or rs1051730 was linked to an upsurge resting heartbeat rate (0.36 bpm/allele; 95% confidence interval 0.18; 0.54). -No strong relation was found with systolic BP, diastolic BP, and HTN.	-No validity data of SNPs was provided in this study. -Its correlation with the commencement of smoking (ie, being an ever versus a never smoker) is not well-established. -It does provide some proof that quitting smoking is related.	The results showed that smoking is directly linked to increase resting heart rate, according to this massive MR meta-analysis, but no casual relation was found between smoking and change in blood pressure.

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Table 3 Summary of the Difference Between Observational and MR Studies

Feature	Observational Studies	Mendelian Randomization Studies
Study design	Cohort, Cross-sectional	Instrumental variable (IV)
Sample size	Large	Moderate
Setting	Real-world	Controlled
Casual inference	Limited	Strong
Susceptible to bias	Yes	Les susceptible
Strength	Large data sets, Real world insights	Overcome confounding, establishes causality
Limitations	Cannot determine causation, susceptible to bias	Involves genetic data, may not be applicable to all exposures

demonstrate a causal relationship between smoking and BP. These studies revealed a minor, yet significant, reduction in both diastolic and systolic BP with every additional pack-year of smoking. Despite the absence of a clear correlation between smoking behavior and HTN, MR studies have indicated that smoking affects intermediate phenotypes and putative mediators that may contribute to the development of HTN.[48,49]

The results of both MR analysis and observational studies generally support a link between smoking and HTN.[21,22] However, disparities were observed. While MR research has not shown a substantial correlation between smoking behavior and hypertension, observational studies have consistently indicated that smoking is associated with an elevated risk of hypertension. These disparities can be attributed to several factors. It is conceivable that smoking influences hypertension through a mechanism different from that mediated by the genetic variations employed in MR investigations. Additionally, there is a possibility that the genetic variations used in MR research may not be reliable indicators of smoking behavior.

Biases and Confounding Factors

The inherent relationship between smoking behavior and the risk of HTN may face distortions due to biases and confounding factors, despite valuable insights observational studies offer into the connections between exposures and outcomes. Biases and confounders may lead to inaccurate conclusions regarding the causal relationship between smoking and HTN.

Selection bias occurs when study participants deviate from the intended audience, potentially causing an overestimation or underestimation of the true relationship between smoking behavior and HTN. For instance, a study relying solely on volunteers may not accurately represent the prevalence of HTN and smoking behaviors in a broader community.

Information bias arises from imprecise or inconsistent measurements of exposure or outcome, leading to participant misclassification and potentially skewing the relationship between smoking behavior and hypertension. Failure to employ objective measures to verify self-reported smoking habits may result in underestimation of the underlying connection.

Confounding variables can obscure or amplify the actual association of interest by introducing additional causal pathways between the exposure and outcome. Variables such as age, sex, BMI, socioeconomic position, and underlying medical disorders may independently affect smoking behavior and HTN in the context of smoking and hypertension, generating erroneous or exaggerated connections.

Robustness of Causal Inferences

By eliminating biases and confounding variables inherent in observational research, MR studies offer a potent method that establishes a robust and reliable framework for determining the causal links between exposure and outcomes. Randomization of genetic variants at conception substantially eliminates selection bias, and the outcomes do not influence exposure. Genetic polymorphisms serve as highly accurate indicators of smoking behavior, eliminating the potential for information bias in self-reported or proxy measurements.[51] Confounding variables are effectively controlled as genetic variants remain unaffected by lifestyle decisions, underlying medical issues, or socioeconomic position.

The consistency of MR inferences relies on crucial assumptions, including exposure linked to the instrumental variables (IVs). Genetic variations associated with smoking behavior should be utilized as IVs in the context of smoking and hypertension (HTN). Exposure should be closely linked to the IVs, and inaccurate or biased estimates of the causal influence may result from a weak IV. It is essential that only exposure causes the IV to impact the outcome, as causal conclusions may be biased if the IV directly affects the outcome. Horizontal pleiotropy, in which IV influences the outcome through multiple channels, can lead to biased causal estimations and erroneous connections.

While MR provides a robust method for drawing conclusions about causality, it is not immune to bias. Reverse causality, where exposure affects the outcome, can distort MR results. The results may also be inflated if a genetic variable linked to smoking behavior influences HTN through a different mechanism. Researchers employ various techniques, such as F-statistics, pleiotropy checks, and sensitivity analysis, to assess the validity of IVs and test the robustness of MR results. Triangulating evidence from both observational and MR studies is crucial to support causal conclusions regarding the relationship between smoking and HTN. Strong evidence for a causal association was derived from consistent results across both types of investigations.

Clinical Implications

Public Health Strategies

The correlation between smoking and HTN risk has noteworthy clinical and public health consequences that demand attention from healthcare practitioners, legislators, and public health organizations. Smoking is substantially correlated with hypertension (HTN), a primary risk factor for cardiovascular disease (CVDs). This relationship has significant clinical implications, contributing to conditions such as heart attack, stroke, chronic renal disease, and other adverse health effects, all exacerbated by HTN. Smoking increases these risks by altering BP. Smoking cessation is an effective measure for mitigating the risk of HTN. Studies have indicated that smoking dramatically lowers blood pressure, thereby minimizing the risk of HTN and its negative effects.[52]

In clinical practice, smokers at high risk of developing HTN should receive comprehensive patient management, incorporating counseling and assistance in quitting. Combined pharmacotherapy, behavioral counseling, and combination approaches have proven effective in this regard.[53]

Campaigns for health education and awareness are crucial in encouraging smoking cessation and enhancing understanding of the harmful effects of smoking on cardiovascular health. These campaigns should tailor their messaging to appeal to various demographics and consider cultural sensitivities. Medical professionals, including doctors, nurses, and other healthcare workers, play a pivotal role in identifying individuals at risk of smoking-related HTN, aiding smoking cessation, and monitoring the blood pressure of smokers. Healthcare providers can assist individuals in quitting smoking and reducing their risk of HTN by assessing smoking history, identifying risk factors, and providing personalized counseling.

The relationship between smoking and HTN underscores the importance of comprehensive public health initiatives aimed at reducing the smoking prevalence and promoting healthy lifestyle choices. Policies related to tobacco control, smoking cessation programs, and health promotion activities should be integral components of these efforts.

Smoking Cessation Interventions

Interventions aimed at quitting smoking are incredibly cost-effective for controlling and preventing HTN, which lowers the cost of healthcare and the burden of the disease. The difficulties and obstacles to quitting smoking, such as social and cultural factors, nicotine addiction, and restricted access to resources for quitting, can be overcome by public health interventions that target smokers at all stages of addiction, from prevention to treatment and relapse prevention.

Hypertension Management

A multimodal strategy involving tobacco control measures, legislative changes, and cooperation between public health organizations, policymakers, and healthcare practitioners is needed to address smoking behavior and HTN. Implementing smoke-free public areas, raising tobacco taxes, limiting tobacco advertising, promoting smoking cessation programs,

launching public awareness campaigns, implementing community-based interventions, and incorporating smoking cessation counselling into routine medical visits are all examples of effective strategies.

Future Research Directions

Unresolved Questions

Future studies examining the relationship between smoking and HTN should prioritize regions where available data are contradictory or unclear. Focusing on areas where the underlying mechanisms are not fully understood and where questions about how smoking habits affect the risk of HTN remain unanswered are crucial. More research is needed to elucidate the role of genetic factors in mediating the link between smoking and HTN, including the impact of smoking on different subtypes of HTN and any variations in the association based on sex.

There is a need to clarify the ways in which oxidative stress and inflammation contribute to the association between smoking and HTN. Understanding the impact of smoking on vascular health and endothelial function in relation to HTN is essential. Additionally, investigating how smoking alters DNA in a manner that promotes HTN development is a critical area for further exploration.

Research efforts should also concentrate on the dose-response relationship between the risk of hypertension and the duration and intensity of smoking. Understanding the effects of smoking cessation on the timing and duration of quitting, as well as the long-term health benefits of smoking cessation on the risk of HTN, is essential.

By addressing these open questions and information gaps, future research can contribute to the development of more efficient preventative measures, individualized treatment plans, and focused interventions. This approach has the potential to reduce the burden of this important public health issue significantly.

Methodological Advancements

Applying methodological innovations to investigate the correlation between smoking and HTN has the potential to significantly enhance our understanding of this intricate relationship. Cutting-edge statistical tools, such as causal mediation analysis and machine learning, can facilitate the thorough investigation of plausible mediators and complex pathways connecting smoking to HTN. These advanced techniques reveal subtle connections, which are often overlooked by traditional methods.

Larger-scale studies and meta-analyses conducted across diverse populations can collaborate to improve statistical power, reduce study heterogeneity, and generate more reliable findings regarding the smoking-HTN relationship. Integrating omics technologies such as transcriptomics, metabolomics, and genomics into research frameworks provides a comprehensive understanding of the underlying biological mechanisms. This integration allows for the identification of biomarkers, genetic variations, and the metabolic pathways involved, opening the door to personalized and targeted interventions.

Together, these analytical advances have broadened our knowledge of the relationship between smoking and HTN, offering new possibilities for public health and intervention methods.

Novel Approaches and Technologies

Research on the link between smoking and HTN has advanced with the advent of new methods and tools. The integration of wearable technology, mobile health applications, and remote monitoring technologies enables continuous monitoring of natural environments. Real-time data on blood pressure variations, smoking patterns, and other pertinent physiological parameters can be collected, providing a more comprehensive understanding of the dynamic relationship between smoking and HTN.

Exploring gene-environment interactions and identifying new genetic variations linked to smoking behavior and susceptibility to hypertension are facilitated by utilizing genetic data from large biobanks and genomic consortia. This wealth of genetic information allows researchers to delve deeper into the molecular mechanisms underlying the association between smoking and HTN.

Customized, scalable methods, such as behavioral therapies including digital health interventions and cognitive-behavioral therapy, play a crucial role in reducing the risk of HTN and promoting smoking cessation in both research and

clinical settings. In addition to facilitating thorough data collection, these cutting-edge techniques and technologies open the door to tailored interventions and a better comprehension of the complex interactions that exist between behavioral patterns, genetic variables, and cardiovascular health outcomes in the context of the association between smoking and HTN.

Conclusion

An extensive body of observational research has consistently demonstrated a link between smoking behaviour and the risk of HTN. However, this association was not supported by causal genetic evidence in (MR) studies. While studies using observational data have consistently indicated a higher incidence of HTN among smokers, MR studies have not provided clear-cut evidence supporting a causal link between smoking and HTN. These conflicting results suggest that smoking alone may not be the sole factor contributing to the association with HTN, and other harmful lifestyle choices may also play a role. Extensive observational and genetic research, particularly for suitable instrumental variable (IV) selection, is necessary to accurately determine the causal relationship between smoking and HTN.

These findings have significant implications for medical professionals and clinical practice. Healthcare clinicians should routinely assess smoking status and provide smoking cessation counselling to all patients with HTN or those at a risk of developing HTN. Routine clinical care should integrate effective smoking cessation strategies, including combination methods, medication, and behavioural counselling. Emphasizing the importance of smoking cessation in overall cardiovascular health and disease prevention is crucial in clinical practice.

Future research efforts should prioritize deciphering the complex molecular and cellular mechanisms underlying smoking-induced hypertension, defining the causal pathways involved, and identifying putative mediators. Investigating the interaction between genetic variables and this correlation is essential for customizing risk evaluation and therapeutic approaches. Longitudinal studies are necessary to evaluate the long-term effects of smoking cessation on cardiovascular and HTN outcomes. Research on cutting-edge interventions, such as behavioral and pharmacological therapies, is crucial for developing more effective preventative and management plans. Addressing these research pathways can strengthen the body of evidence, improve therapies, and reduce the significant health burden associated with smoking and the risk of HTN.

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