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Review

Assessing Nicotine Pharmacokinetics of New-Generation Tobacco Products and Conventional Cigarettes: A Systematic Review and Meta-analysis

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Abstract

Introduction: New-generation tobacco products (NGPs) hold promises as modified-risk alternatives to conventional cigarettes (CCs), given their comparable characteristics. This study investigated the nicotine pharmacokinetics (PK) of NGPs, encompassing closed pod systems, refillable e-cigarettes (ECs), and heated tobacco products (HTPs), in comparison to CCs through systematic review and meta-analysis.

Aims and Methods: A comprehensive search was conducted on PubMed, Embase, and Web of Science for articles published between January 2013 and July 2023. Maximum nicotine concentration (C_{max}), time to peak concentration (T_{max}), and total nicotine exposure (area under the concentration-time curve, AUC) were extracted to evaluate nicotine delivery PK. Random effects meta-analyses were performed to determine pooled standardized mean differences, facilitating a comparison of PK profiles between NGPs and CCs. Subgroup analyses exploring flavors and nicotine concentrations across NGPs, and CCs were also conducted.

Results: The meta-analysis incorporated 30 articles with 2728 participants. C_{max} and AUC were significantly lower for NGPs, while T_{max} demonstrated statistical similarity compared to CCs. Among three NGPs, C_{max} and AUC were lower for closed pod systems and refillable ECs. In HTPs, C_{max} was statistically similar while AUC was lower compared to CCs. T_{max} was statistically similar in closed pod systems and HTPs compared to that of CCs. No significant difference was observed in the comparisons of PK between each type of NGPs versus CCs.

Conclusions: NGPs delivered less nicotine than CCs but reached C_{max} over a similar timeframe, indicating that NGPs may serve as modified-risk alternatives with lower nicotine delivery to CCs for craving relief and smoking cessation.

Implications: This study suggested that NGPs, such as the closed pod systems, the refillable ECs, and the HTPs, delivered either lower or comparable nicotine levels and achieved peak nicotine concentration at a similar rate as CCs. Our findings carry implications that NGPs can serve as modified-risk nicotine alternatives to CCs in helping smokers manage cravings and potentially quit smoking, thereby highlighting their value in the field of tobacco harm reduction.

Introduction

Smoking is widely acknowledged as a significant public health hazard, closely associated with various chronic diseases and an increased risk of premature mortality.[1] Previous research has demonstrated that the elevated mortality rate attributed to smoking predominantly manifests in respiratory, cardiovascular diseases, and cancer.[2–4] Tobacco use amplifies mortality from pneumococcal pneumonia, with smokers exhibiting a 0.6% higher mortality rate than nonsmokers at 30 days.[5] Smoking is identified as the primary risk factor for coronary heart disease, with a long-lasting impact extending to approximately 0 years.[6] A meta-analysis pointed out that smokers have a 13% increased risk of developing breast cancer compared to nonsmokers in prospective studies,[7] and smoking is responsible for approximately 63.17% of all lung cancer deaths.[8]

Traditionally, conventional tobacco products have been the predominant source of smoking, but in recent years, there has been a global proliferation of New-Generation Tobacco Products (NGPs).[9,10] NGPs include closed pod systems, refillable e-cigarettes (ECs), and heated tobacco products (HTPs).

Closed pod systems and refillable ECs generate vapor through heating rather than combustion, thereby avoiding the production of harmful combustion-related substances, potentially reducing the inhalation of harmful chemicals.[11] HTPs operate by generating aerosols by heating tobacco without combustion, further mitigating the production of harmful combustion-related chemicals.[12]

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When evaluating the propensity for nicotine abuse, the pharmacokinetic characteristics of nicotine need to be considered. Abuse liability refers to the potential for a substance, such as nicotine, to be misused or lead to addiction.[13] A higher C_{max} may indicate stronger reinforcement and addictive potential. A higher C_{max} suggests a more rapid delivery of nicotine to the brain, leading to pronounced pharmacological effects and potentially stronger reinforcement of the drug's rewarding properties. Similarly, a larger AUC may increase the propensity for abuse. A larger AUC signifies prolonged exposure to nicotine, which may enhance the reinforcing effects of the drug. A shorter T_{max} indicates an earlier peak concentration of nicotine, which may lead to faster interaction and satisfaction with the reward circuit. This may increase the propensity for nicotine abuse, as instant gratification is associated with enhanced addictive potential. In a randomized, controlled, open-label, crossover study, the cigarette showed greater nicotine uptake (C_{max} = 22.7 ng/mL) in conventional cigarettes (CCs) compared to NGPs (8.6 and 10.5 ng/mL). The median T_{max} for nicotine replacement therapies (15.03 minutes) was significantly longer than CCs (4.05–6.03 minutes). Besides, CCs have the highest product preference and overall intent for repeated use and can reduce smoking urges more effectively than other products. This indicates that the abuse liability of NGPs is lower than that of regular-brand cigarettes.[14]

Previous studies have provided preliminary insights into the pharmacokinetics of NGPs and CCs. They pointed out the pharmacokinetics features of the three most common types of NGPs. For instance, compared to e-cigarettes, CCs were associated with greater C_{max} (25.9 vs. 9.0, p = .0043) and greater nicotine boost (21.0 vs. 8.2, p = .0128).[15] Another study found that e-cigarettes, after inhaling the same nicotine amount, resulted in lower blood nicotine concentrations (13.19 ± 9.03 ng/mL) compared to CCs (16.05 ± 10.21 ng/mL).[16] Moreover, the release rate of nicotine in e-cigarette aerosols was reported to be faster than that of CCs in a different study.[17] Additionally, HNB products were found to produce significantly lower levels of nicotine and harmful and potentially harmful constituents compared to CCs.[18] Closed pod systems exhibited lower aerosol concentrations than open systems in terms of nicotine.[19]

Despite these valuable contributions, limitations such as variations in sample size, study design, and data analysis methods exist. There is no consensus on the differences in pharmacokinetics between NGPs and CCs. Therefore, this systematic review and meta-analysis aim to synthesize existing studies, providing a comprehensive understanding of pharmacokinetic disparities between NGPs and CCs.

Methods

This systematic review covers data spanning from January 1, 2013, to July 20, 2023. The databases searched include Embase, Web of Science, and PubMed. We registered the research protocol with PROSPERO (CRD42023449750). Two investigators (Y.C. and X.L.) independently undertook the literature search, assessment for eligibility, data extraction, and qualitative assessment. Discrepancies between reviewers were resolved by a third investigator (L.Z.) until consensus was achieved.

Inclusion Criteria

Our research encompassed all clinical trials exploring nicotine characteristics in NGPs and CCs. We then excluded numerous clinical trials that did not encompass complete pharmacokinetic curves but rather focused on nicotine exposure or solely C_{max}. The study focused on diverse age groups, genders, continents, and populations using specific tobacco products, and documented flavors and nicotine concentrations. Our measurement metric is to compare the PK characteristics of nicotine between NGPs and CCs, including maximum nicotine concentration (C_{max}), time to the peak concentration (T_{max}), and total nicotine exposure (area under the concentration-time curve, AUC). The article types included only full-text articles published in academic journals, with conference abstracts and book chapters excluded.

Screening, Data Extraction, and Risk of Bias Assessments

A systematic literature search collected relevant research articles, and two researchers (Y.C. and X.L.) independently assessed titles and abstracts for alignment with the research purpose and inclusion criteria. Nicotine Subject Heading terms were used in conjunction with the following keywords for our search: ("electronic cigarette" or "e-cigarette" or "vape" or "refillable electronic cigarette" or "HTP" or "heat-not-burn") and ([pharmacokinetics or PK].mp. [mp = title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]). We have limited the search time from January 1, 2013, to July 20, 2023. Full search strings are presented in Table S1. We obtained the full text of the remaining articles for final screening. Any inconsistencies were resolved by a third investigator (L.Z.) till a consensus was reached.

Data Extraction

A data extraction table was developed, and essential information, including author, publication date, participant characteristics, comparative groups, outcome indicators, and other features, was extracted independently by two researchers.

The flavors extracted from diverse literature sources encompassed BIDI Stick Arctic, BIDI Stick Classic, BIDI Stick Regal, BIDI Stick Solar, BIDI Stick Winter, Blond, classic, freebase, Fusion, lactate, Mint, original, tobacco, unflavored, and Virginia Tobacco. These flavors were systematically classified into three distinct categories, as follows:

1. Traditional Tobacco Flavor: BIDI Stick Classic, Blond, tobacco, classic, freebase, Virginia Tobacco.
2. Mint Flavor: BIDI Stick Arctic, Mint.
3. Other Flavors: BIDI Stick Regal, BIDI Stick Solar, BIDI Stick Winter, lactate, original, unflavored.

We have also collected different nicotine concentrations in the literature. Nicotine can be classified according to its high, medium, and low concentrations.

1. High level: larger than 50 mg/mL.
2. Medium level: 10–50 mg/mL.
3. Low level: smaller than 10 mg/mL.

Data Processing and Analysis

After completing the data extraction, we carefully reviewed and organized the extracted data, and organized it in the data

extraction table. The table contains relevant details such as author, publication date, participant characteristics, comparative groups, outcome indicators, and other important features. Full details can be found in Table S2. Throughout the entire data processing and analysis process, we strove to ensure transparency, reliability, and effectiveness. All steps were carried out by two independent researchers (Y.C. and X.L.). Any inconsistencies between the reviewers were resolved by a third investigator (L.Z.) till a consensus was reached.

We converted the data as needed to ensure consistency and comparability. For data that only provides the median range in the articles, we used the est means package in R language to convert it to the mean (standard deviation). By applying the "est. mean.sd()" function in the package, we estimated the average and standard deviation of the data and ensured that the parameters were set appropriately (for example, "rangeknow=TRUE"). For data that provides a median (coefficient of variation), we used the bootstrap method in R language[20] for resampling and converted the median (coefficient of variation) to the mean (standard deviation). By repeatedly sampling and calculating the mean and standard deviation for each sampling, we obtained multiple estimates. By calculating the mean and standard deviation of these estimates, we obtained the final estimated result. Then we converted the sorted effect size into standardized mean differences (SMD). This transformation helps to enhance data comparability and allows for more intuitive comparison and synthesis of research results.

Given the significant heterogeneity owing to a diversity of study designs or methodological differences in the included studies, we established a random-effect model to estimate aggregated effects using SMD with its 95% confidence intervals (CI). The random-effect model can take into consideration the heterogeneity between and within studies, allowing each study to have its own effect size and address the variability between these effects. The degree of heterogeneity within the pooled studies was assessed through Q-statistics and I^2 statistics. In addition, we conducted a subgroup analysis to further explore potential sources of heterogeneity. Forest plots were drawn to display the magnitude of the pooled effect during the whole process. We evaluated the existence of publication bias by visually examining funnel plots and using statistical tests such as Egger's regression tests. All p values were two-sided, and $p < .05$ was considered statistically significant. All data analysis was conducted using statistical software (R 4.2.2).

Bias Risk Assessment

We used the Cochrane risk bias tool to assess the bias risk included in the study.[21] This includes randomization process bias, execution bias, reporting bias, and other potential sources of bias. Two independent researchers conducted a bias risk assessment independently and assessed the quality of the studies based on the guidelines in standardized tools. Figure S1 summarizes the overall bias of this study.

Results

In the 30 existing articles measuring nicotine PK (Figure 1),[15,16,22–49] we compared C_{max}, T_{max}, and AUC of three types of NGPs, including closed pod systems, refillable ECs, and HTPs with those of CCs. We also conducted the subgroup analysis by different flavors and nicotine concentrations of NGPs and CCs, as well as age, gender, and continent characteristics.

Pooled SMD in C_{max} Between Three Types of NGPs and CCs

C_{max} was found to be significantly lower in NGPs compared to that in CCs (SMD = –3.09, 95% CI: [–5.6, –0.57], $p = .02$) shown in the forest plot of Figure 2. Meanwhile, there was no significant difference when comparing nicotine PK profiles between each type of NGPs versus CCs ($X^2 = 2.45$, $p = .29$). However, closed pod systems and refillable ECs showed a significantly lower trend C_{max} in NGPs. There was no statistical difference between HTPs and CCs in C_{max}.

Pooled SMD in T_{max} Between Three Types of NGPs and CCs

There was no statistically significant difference between NGPs and CCs in T_{max} general (SMD = 0.21, 95% CI: [–0.54, 0.96], $p = .58$), as shown in Figure 3. There was no significant difference in subgroup analysis among different types of NGPs versus CCs in T_{max} ($X^2 = 0.66$, $p = .72$).

Pooled SMD in AUC Between Three Types of NGPs and CCs

In general, the AUC of nicotine PK was significantly lower in NGPs than those in CCs (SMD = –3.33, 95% CI: [–5.22, –1.44], $p < .01$) as shown in Figure 4. Among the three types of NGPs, there was no significant difference among each type of NGPs versus CCs in AUC ($X^2 = 4.55$, $p = .10$).

Subgroup analyses were undertaken based on variations in flavors and nicotine concentrations. Figures S2 and S3 present the detailed results of these subgroup analyses. There was no statistically significant difference in overall C_{max} (SMD = –4.54, 95% CI: [–9.76,–1.44], $p = .09$), T_{max} (SMD = –0.54, 95% CI: [–3.93, 2.85], $p = .75$) and AUC (SMD = –4.36, 95% CI: [–9.72, 0.40], $p = .07$) between each type of NGPs and CCs by flavors. In the Mint flavor, the C_{max} (SMD = -0.38, 95% CI: [–9.76, –1.44]) was significantly lower, and in the traditional tobacco flavor, the AUC (SMD = –1.10, 95% CI: [–1.50, –0.69]) showed a lower level compared with CCs.

There was no statistically significant difference in T_{max} (SMD = 0.13, 95% CI: [–1.17, 1.43], $p = .09$) between NGPS and CCs by nicotine concentration.

Besides, in the high level of nicotine concentration, C_{max} (SMD = –2.77, 95% CI: [–5.06, –0.48]) was found to be significantly lower in NGPs than that of CCs, while in the median level of nicotine concentration, AUC (SMD = –5.10, 95% CI: [–8.73, –1.46]) was significantly lower in NGPs than that of CCs.

In addition, we also conducted comparisons with age, gender, and geographical regions as subgroups. According to our subgroup analysis results, age, gender, and continent may have certain effects on the PK parameters of nicotine. Different age groups showed similar T_{max} values and had a lower level of C_{max} and AUC while using NGPs compared with CCs. Similarly, gender differences also lead to lower-level values in C_{max} and AUC, the T_{max} had no statistical difference according to different genders between NGPs and CCs. Meanwhile, there were statistical differences between different geographical continents in C_{max} and AUC, resulting in a lower level in NGPs compared with CCs, which may be related to the different consumption habits and nicotine intake of different tobacco products in different areas. All subgroup meta-analyses can be seen in Figure S4 to S12.

Egger's test was conducted to assess the presence of publication bias for each category in the analysis, as shown in

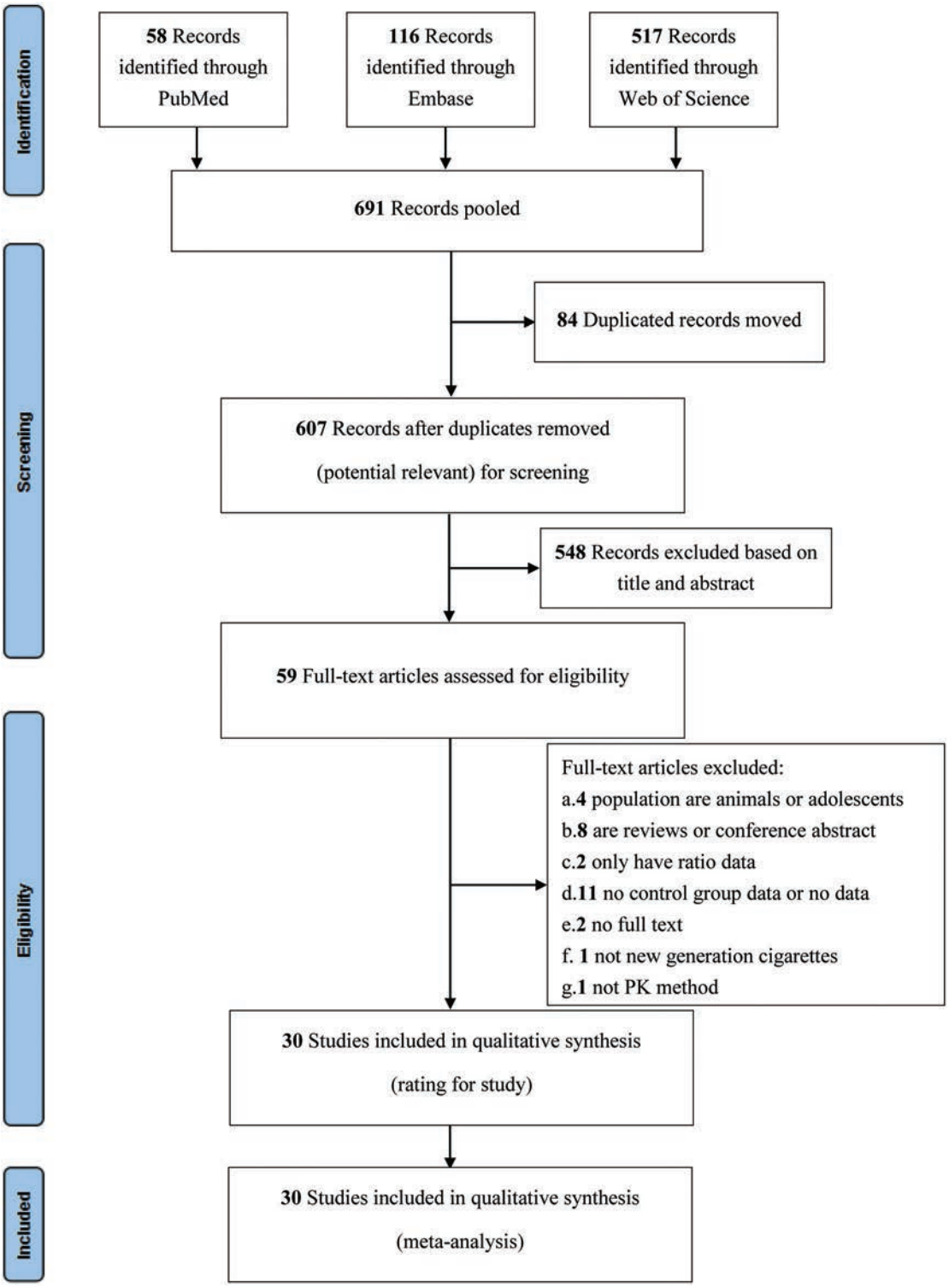

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses)[25] Flow diagram.

Figure 5, revealing a presence of publication bias ($p < .05$), and suggesting the possibility of selective reporting or publication of studies, which may introduce bias in the overall understanding of the research topics.

Discussion

In this study, we conducted a systematic review and meta-analysis to compare the nicotine PK parameters, including C_{max}, T_{max}, and AUC between each type of NGPs and CCs.

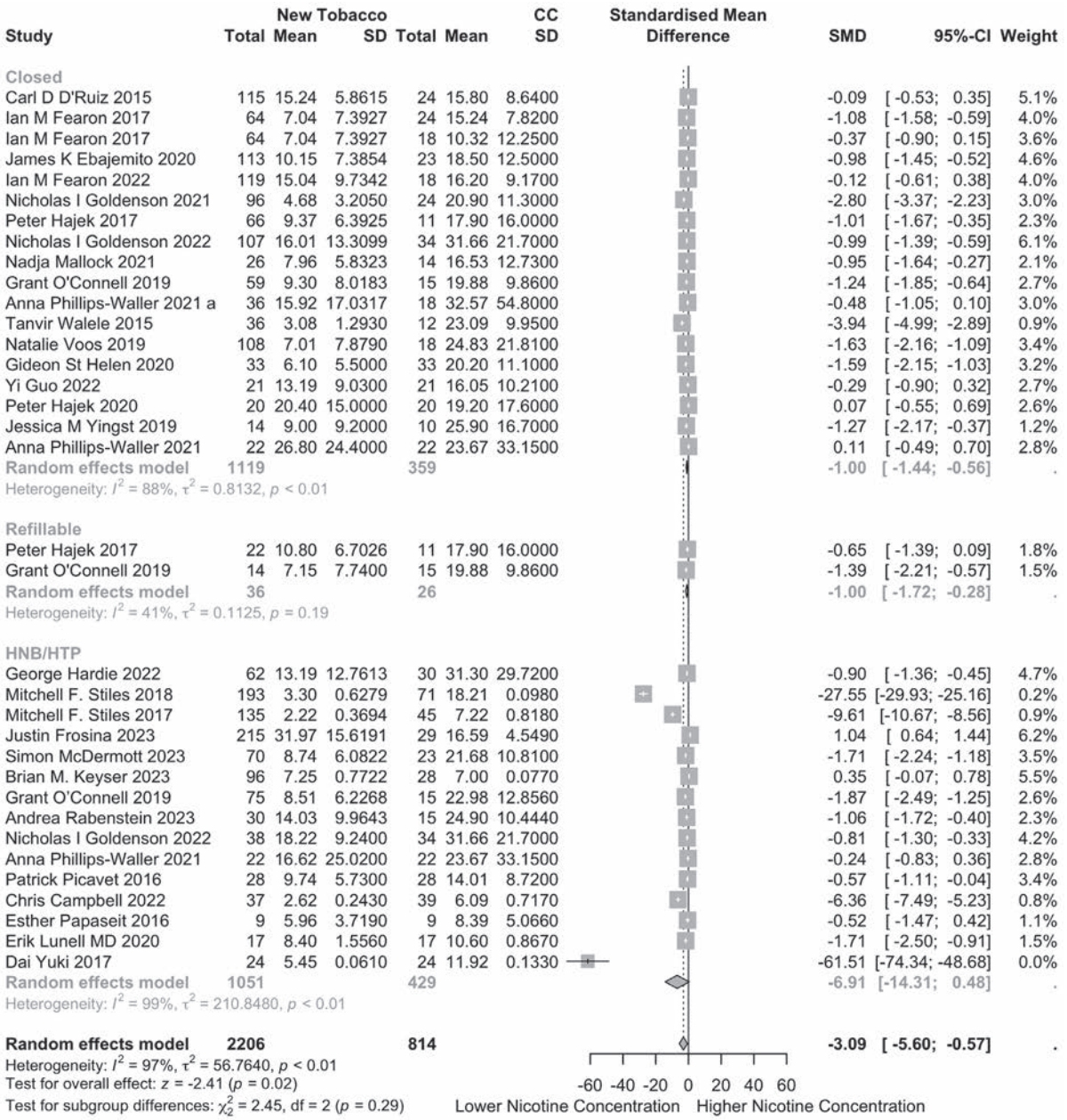

Figure 2. Forest plot of meta-analysis standardized mean difference in C_{max} between three types of new-generation tobacco products and conventional cigarettes (CCs). The size of the plotted squares reflects the relative statistical weight of each study. The numbers on the *x*-axis denote the standardized mean differences. The horizontal lines denote the respective 95% confidence intervals (CI).

These results provide important insights into the comparative of NGPs and CCs, especially in terms of nicotine delivery. Insignificantly lower C_{max} suggested that NGPs may offer a potentially less intense nicotine experience compared to CCs.[24] This lower level of C_{max} cannot provide them with the required nicotine levels but can be less addictive. Lower nicotine peak concentrations may lead to lower euphoric and habit-strengthening effects, thereby reducing the need for rapid nicotine satisfaction. This helps smokers gradually reduce nicotine intake, reduce nicotine addiction and dependence, and thus provide the possibility of smoking cessation. However, it is important to take other factors such as overall nicotine exposure and individual usage patterns into account, as they may impact the overall effects of NGPs on nicotine consumption. Among them, there is no evidence that HNB has significant statistical differences in C_{max} compared with that of CCs, which may be caused by three factors. First, different types of electronic cigarette devices have different designs and working principles. The design or use of closed pod systems and refillable e-cigarettes may result in a lower level in the rate and degree of nicotine release, thereby affecting nicotine concentration. Since the working principle of HNB differs from other types of e-cigarettes, this may lead to an absence of a significant difference in nicotine concentration.

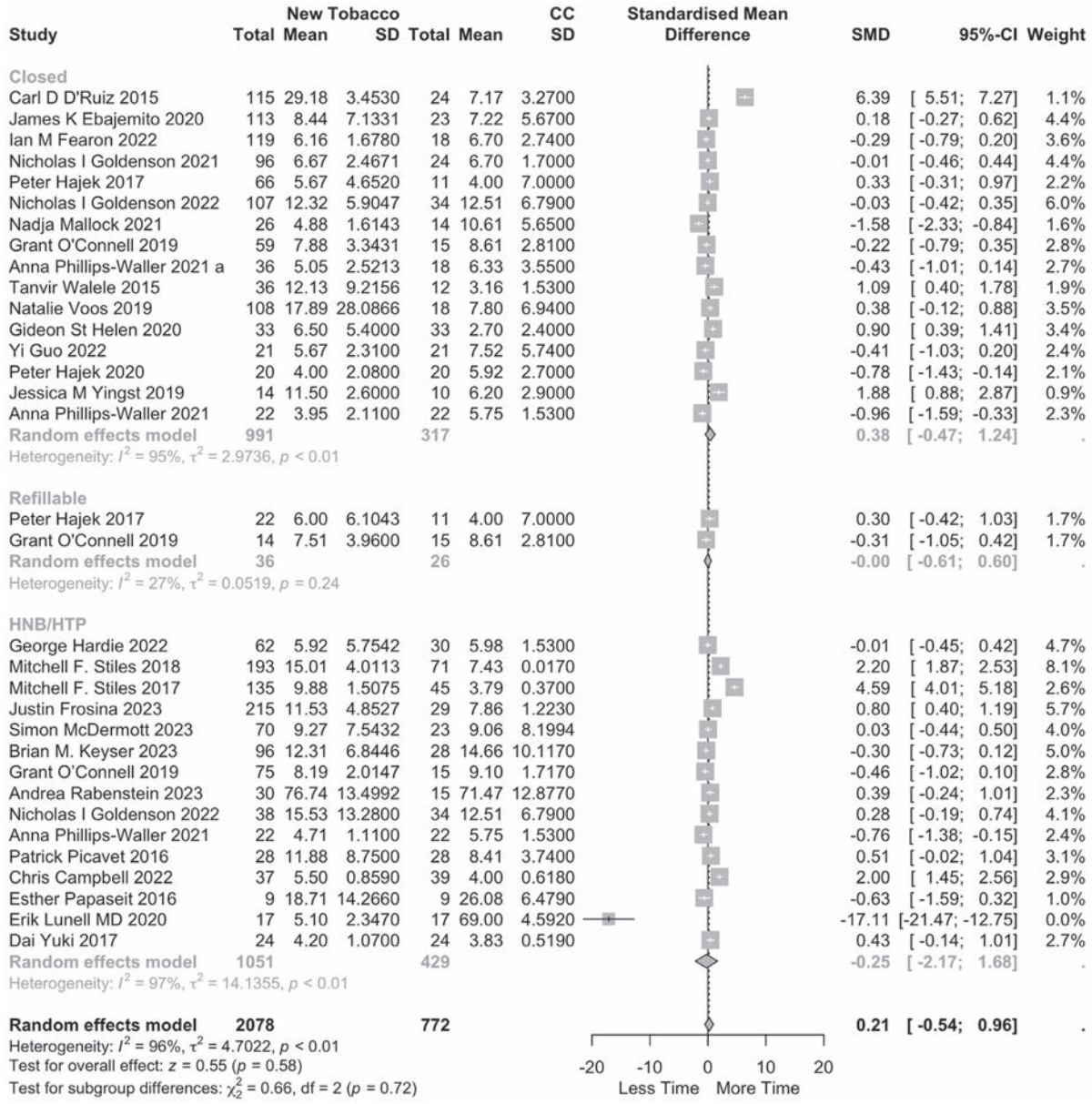

Figure 3. Forest plot of meta-analysis standardized mean difference in T_{max} between three types of new-generation tobacco products and conventional cigarettes (CCs).

Meanwhile, the result is based on data from different studies. The differences in sample size, sample population, and data collection and analysis methods of the study may affect the significance of the results.

On the other hand, there is a lower level of AUC in NGPs compared to CCs. This outcome indicates that NGPs provide an overall lower exposure to nicotine over time. The potential benefit of this in AUC is two-fold. Firstly, it may contribute to harm reduction strategies by minimizing the adverse health effects associated with prolonged nicotine exposure.[27] Secondly, it could aid in smoking cessation efforts, as lower levels of nicotine exposure may help individuals gradually reduce their nicotine dependence. The AUC may effectively reduce the immediate satisfaction and strengthening effect of nicotine, thereby reducing the tendency towards abuse. Nonetheless, additional research is needed to fully understand the implications of these findings on nicotine dependence and long-term health outcomes.

According to our research results, the new device and traditional tobacco exhibit similarity in T_{max}, which suggests that the NGPs and CCs may have similar effects in terms of detoxification. Therefore, we can conclude that the NGPs are potentially fewer addictive alternatives that can assist smokers in alleviating their tobacco cravings and even achieving their smoking cessation goals. This discovery supports the similarity between the NGPs and CCs in terms of addiction relief, providing smokers with a safer choice.

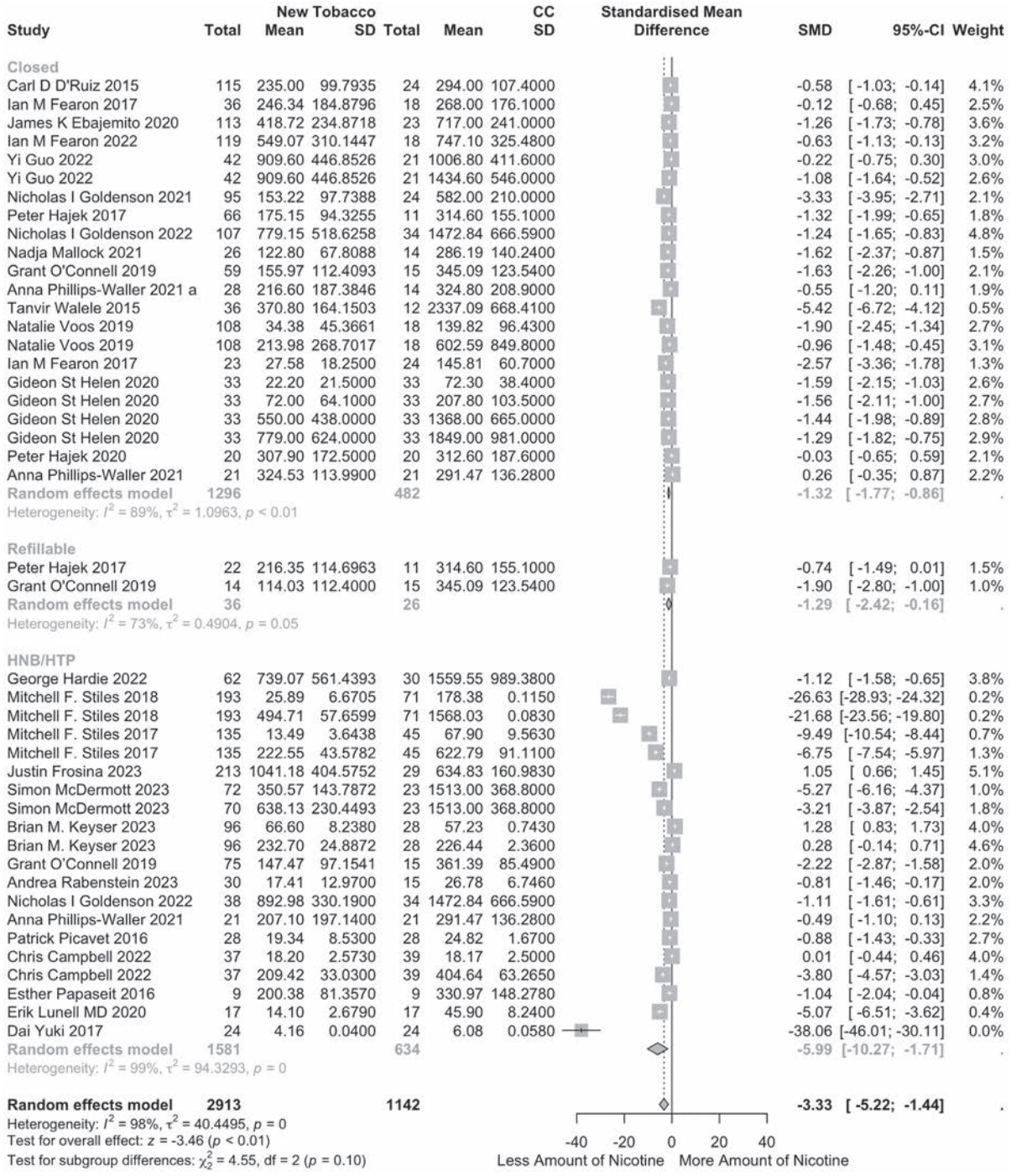

Figure 4. Forest plot of meta-analysis standardized mean difference in area under the curve between three types of new-generation tobacco products and conventional cigarettes (CCs).

NGPs can potentially serve as modified-risk with lower nicotine delivery and less addictive alternatives to CCs in helping smokers manage cravings and quit smoking. Besides, abuse liability needs to be assessed from both the perspectives of pharmacokinetics (PK) and subjective effects. Past literature also indicates that, when considering these two aspects, the data obtained in Tobacco Heating Products demonstrate a lower abuse liability than that of participants' usual brand cigarettes. Nicotine delivery and the reduction of the urge to smoke/vape upon usage of NGPs were lower in comparison to CCs.[14,50]

For products with three different flavors (mint, traditional tobacco, other), the overall C_{max}, T_{max}, and AUC were not statistically different between NGPs and CCs ($p > .05$). This

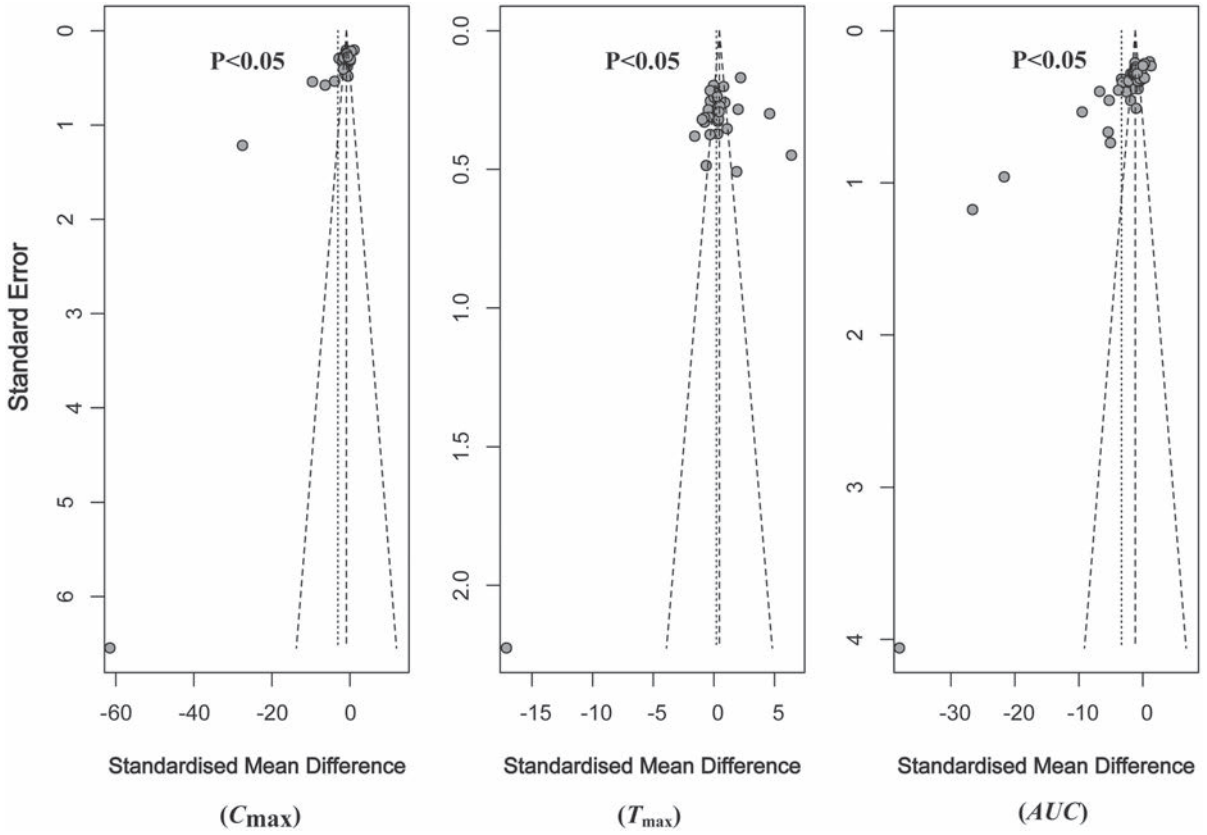

Figure 5. Funnel plots for publication bias of included studies in the analysis.

means that there is no significant difference in pharmacokinetic parameters between NGPS and CCs in terms of each type of flavors. However, when observing the mint flavor alone, the C_{max} has a significantly low value, which may indicate a lower level of nicotine absorption in mint-flavored NGPs compared to traditional tobacco products. In addition, the low value of AUC in traditional tobacco flavored products means that the overall absorption of nicotine is relatively low compared to traditional tobacco products. It should be noted that although significant differences were found in certain flavors, no significant differences were found overall. This may be due to sample size limitations, so the results have not yet reached a significance level.

Under different concentrations of nicotine, the C_{max} and AUC of NGPs were lower compared to traditional tobacco. This means that regardless of nicotine concentration, new tobacco products exhibit lower results in terms of the highest peak concentration (C_{max}) and area under the curve (AUC) of nicotine in plasma compared to traditional tobacco. Lower C_{max} and AUC may mean that new tobacco products provide less nicotine absorption compared to traditional tobacco, or are metabolized and cleared faster. This may be related to factors such as the design, composition differences, and nicotine delivery methods of new tobacco products.

It is important to acknowledge that our analysis focused on specific product categories and factors such as nicotine concentration, flavor, and demographic characteristics while excluding certain product characteristics like e-cig power and formulation. These additional product attributes have been recognized as potential influencers of nicotine C_{max}/T_{max}/AUC, and their exclusion from our subanalyses represents a limitation of the study. Future research should aim to incorporate a broader range of product characteristics to provide a more holistic understanding of the factors impacting nicotine pharmacokinetics in NGPs and CCs. Additionally, the absence of data on certain product characteristics may have implications for the generalizability of our findings and should be considered when interpreting the results. Addressing these limitations and exploring a more comprehensive set of product attributes in future studies will contribute to a more robust assessment of nicotine delivery profiles and enhance the validity and applicability of our findings.

The categorization into three levels allowed for a systematic analysis of the impact of varying nicotine concentrations on pharmacokinetic outcomes, even though specific data on low nicotine concentrations was limited. Future research may benefit from including a broader range of nicotine concentrations to provide a more comprehensive understanding of nicotine delivery profiles in electronic cigarettes and HTPs.

The results of subgroup analysis showed that no significant differences were observed between the three different types of new tobacco (HNB/HTP, refillable, and closed) in terms of maximum nicotine concentration (C_{max}), time to peak concentration (T_{max}), and total nicotine exposure (AUC) compared to CCs. This is an important research finding indicating that the nicotine released by NGPs is similar in terms of absorption rate and overall exposure with CCs. The comparatively modest nicotine release and akin release rates observed in

novel tobacco products present potential avenues for aiding smokers in transitioning away from CCs, thereby facilitating reductions in nicotine intake and, conceivably, fostering smoking cessation. The diminished nicotine release associated with these innovative tobacco products implies a lesser extent of nicotine absorption in comparison to traditional cigarettes. These characteristics hold promise for assisting smokers in the gradual reduction of nicotine dependence and the stepwise reduction of overall nicotine consumption. Consequently, the distinctive nicotine release profile of new tobacco products may contribute to effective strategies for harm reduction and smoking cessation.

A parallel release rate signifies that new tobacco products exhibit a nicotine delivery rate akin to traditional cigarettes, a factor deemed significant for smokers familiar with the inhalation rhythm and satisfaction associated with conventional smoking habits. The novel generation of tobacco products, by maintaining a similar release rate, can effectively reduce nicotine intake while concurrently addressing the oral and gestural needs inherent to smoking behavior.

The utilization of these new-generation tobacco products holds promise for assisting smokers in gradually diminishing their nicotine dependence and progressing toward the overarching goal of smoking cessation. It is conceivable that diverse types of emerging e-cigarettes may evolve as potential reduced-risk alternatives to traditional tobacco products in the future. However, comprehensive research efforts and regulatory measures are imperative to comprehend and evaluate the full spectrum of potential benefits and risks associated with these nascent products.

Our decision to focus on these NGPs was based on their prevalence in the market, which allowed for robust data collection and comparison in our analysis of nicotine pharmacokinetics. We recognize that there are other types of e-cigarettes available and understand the importance of considering a broader range of e-cigarette products in future studies to provide a comprehensive assessment of nicotine delivery profiles.

In terms of limitations, our meta-analysis was contingent on synthesizing data from diverse studies, introducing inherent heterogeneity and potential biases. Moreover, divergent methodologies, participant characteristics, and tobacco product formulations across the included studies may have contributed to observed variations, necessitating caution in generalizing findings to all NGPs or specific NGP types. However, it is noteworthy that among the 30 included studies, a consistently high level of quality was observed. Rigorous planning and execution of experimental design and data analysis were evident, contributing to the robustness of our findings.

Besides, our study may have introduced bias by excluding studies that reported only C_{max} or nicotine exposure data instead of a full PK analysis. The omission of such studies may have overlooked important information related to electronic cigarettes/HTPs versus CCs. The results of the study should be interpreted cautiously when it comes to generalizability.

The selection criteria for this study focused on studies that conducted a full PK analysis of nicotine in ECs/HTPs and CCs. This criterion may have excluded studies that solely evaluated nicotine exposure or reported C_{max} values due to funding constraints or other reasons.

The exclusion of articles that did not conduct a full PK curve analysis may have limited the breadth of studies included in our analysis and potentially introduced bias. Future research should consider a more inclusive approach to encompass studies with varying degrees of PK analysis to provide a more comprehensive overview of nicotine delivery profiles across different e-cigarette and heated tobacco product (HTP) brands.

To address these limitations, future research endeavors should focus on exploring the intricate pharmacokinetics of NGPs in more depth. Large-scale, well-designed studies are imperative to investigate additional factors influencing nicotine delivery, including user behavior, device design, and specific characteristics of NGP formulations. Longitudinal studies assessing the enduring effects of NGP use on nicotine dependence, smoking cessation, and overall health outcomes are warranted.

Furthermore, while our analysis provides valuable insights into pharmacokinetic differences between NGPs and CCs, it is essential to acknowledge that the assessment of nicotine exposure entails various factors beyond C_{max} and AUC. Consideration of additional study parameters, such as nicotine uptake, elimination half-life, and subjective assessments of nicotine satisfaction, is crucial for obtaining a comprehensive understanding of NGP characteristics.

In discussing the absorption of nicotine in NGPs, it is important to consider the two main pathways, namely absorption through the oral mucosa and the nasal mucosa. The literature suggests that absorption by the oral mucosa is highly pH dependent, while various types of NGPs and devices introduce variability in nicotine absorption. Although individual studies may not delve deeply into specific details on these pathways, our analysis synthesized available information to provide a comprehensive overview.

In conclusion, our meta-analysis findings demonstrate that NGPs generally exhibit similar T_{max} and a lower C_{max} and AUC, suggesting modified nicotine delivery profiles compared to CCs. These findings have important implications for harm reduction strategies and smoking cessation efforts. Meanwhile, the research also found that no significant differences were observed between the three different types of new tobacco (HNB/HTP, refillable, and closed), which indicates that different types of NGPs may become modified-risk substitutes for CCs. However, further research is necessary to validate and expand on these results, considering the diverse landscape of NGP products and users.

The outcomes of this investigation are poised to bridge existing gaps in knowledge pertaining to the comparative pharmacokinetics of NGPs and CCs. These findings carry substantive value for decision-makers in the formulation of informed policies. A nuanced comprehension of the pharmaceutical attributes of NGPs facilitates a more comprehensive evaluation of their potential health risks and impacts relative to CCs. Such insights are pivotal for the development of effective smoking control strategies and the formulation of evidence-based public health policies related to NGPs.

Conclusions

All three types of NGPs delivered less nicotine than CCs but reached the C_{max} over a similar period of time, indicating that NGPs are likely to serve as a less addictive alternative to CCs to assist smokers in craving relief and smoking cessation. This study contributes essential information to the epidemiological understanding of tobacco product dynamics, providing a

foundation for evidence-driven interventions in the realm of tobacco control and public health.

Supplementary material

Supplementary material is available at *Nicotine and Tobacco Research* online.

Acknowledgments

The authors would like to acknowledge the authors for sharing their additional data in our meta-analysis.

Conflicts of Interest

Xiaona Liu, Yue Cao, Zhongyi Hu, Jiaxuan Li, Xi Chen, Yuming Xiong, Fangzhen Zheng, and Jianqiang Zhang are employees of Shenzhen Smoore Technology Ltd, a manufacturer and distributor of e-cigarette products. Lin Zhang and Xinru Liu have no competing interests to declare.

Authors' Contributions

Yue Cao (Data curation [equal], Software [equal], Visualization [equal], Writing—review & editing [lead]), Xinru Liu (Data curation [equal], Software [lead], Visualization [equal], Writing—original draft [lead]), Zhongyi Hu (Writing—review & editing [supporting]), Jiaxuan Li (Writing—review & editing [supporting]), Xi Chen (Writing—review & editing [supporting]), Yuming Xiong (Writing—review & editing [supporting]), Fangzhen Zheng (Writing—review & editing [supporting]), jianqiang Zhang (Writing—review & editing [supporting]), Lin Zhang (Conceptualization [lead], Formal analysis [supporting], Methodology [equal], Project administration [equal], Resources [lead], Supervision [lead], Writing—review & editing [lead]), and Xiaona Liu (Conceptualization [lead], Methodology [equal], Resources [lead], Supervision [equal], Validation [equal], Writing—review & editing [lead]).

Data Availability

The data underlying this article are available in the article and in its Supplementary Material.

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