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IM - REVIEW

Heated tobacco products vs conventional cigarettes: a scoping review of cardiovascular and respiratory clinical outcomes

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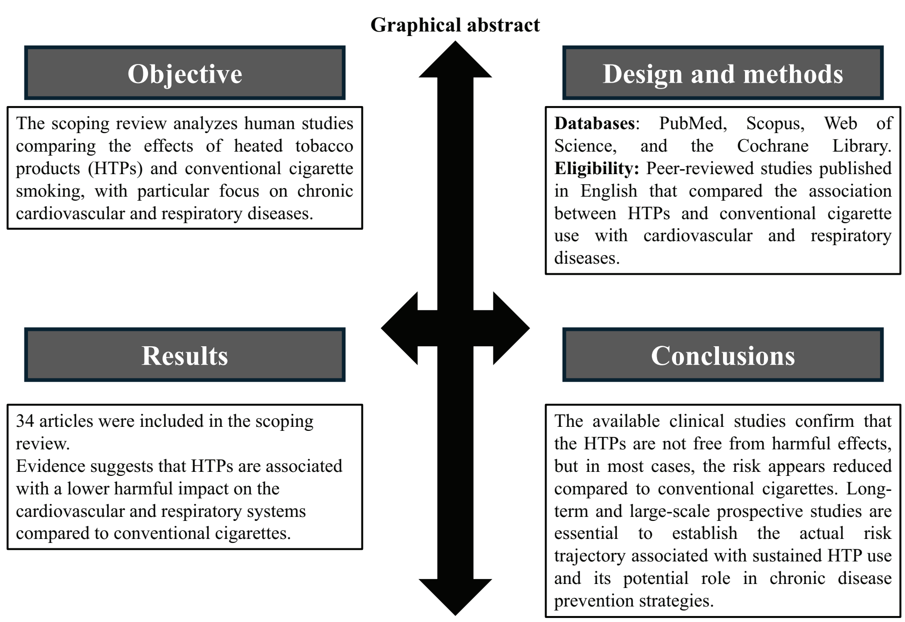
Abstract

The primary objective of this article is to provide an overview of studies in humans that evaluate and compare the effects of heated tobacco products (HTPs) with those of conventional cigarette smoking on cardiovascular and respiratory diseases. To address this research question, a scoping review methodology was employed.

A comprehensive literature search was conducted in the PubMed, Scopus, Web of Science, and Cochrane Library databases to identify relevant articles published between January 2014 and March 2025. Two reviewers independently screened all articles. This process resulted in the identification of 34 articles deemed appropriate to the aims of this scoping review.

Despite the heterogeneity of the available data, the current evidence suggests that HTPs are associated with a lower harmful impact on the cardiovascular and respiratory systems as compared to conventional cigarettes. However, considering the relatively recent introduction of HTPs, in contrast to the long latency periods typically required for the development of smoking-related chronic diseases, as well as the evolving design and composition of these products, it is not surprising that definitive conclusions regarding their clinical, and public health impact bring up the need to be integrated by long-term evidence derived from independently conducted studies.

Graphical Abstract



Keywords Heated tobacco products · Conventional cigarettes smoking · Harm reduction · Global public health

Extended author information available on the last page of the article

Introduction

Tobacco smoking remains one of the leading causes of mortality worldwide and continues to be one of the major modifiable risk factors for global public health. Despite an extensive body of evidence demonstrating the harmful effects of both active and passive exposure to tobacco smoke, efforts to reduce smoking initiation and increase smoking cessation remain significant challenges in reducing smoking prevalence and improving public health [1–3]. To mitigate the harmful effects of smoking and to deliver nicotine in a form deemed less harmful, several novel products have been developed in the recent years. One of the most notable developments in this regard is the introduction of heated tobacco products (HTPs) as an alternative to conventional cigarettes.

Unlike conventional cigarettes, HTPs function by heating tobacco through a battery-powered device that strictly regulates the temperature to which the tobacco is heated. Depending on the product, HTP units typically operate within a controlled temperature range that can reach up to approximately 350 °C, whereas conventional cigarettes burn tobacco at around 800 °C. This reduced heating is thought to produce aerosols containing significantly lower concentrations of toxicants [4].

Cigarette smoking is a well-established risk factor for the development and exacerbation of respiratory and cardiovascular diseases [5]. Cells continuously produce reactive oxygen species (ROS) and antioxidant molecules at the cellular level under normal physiological conditions to maintain redox homeostasis. However, the chemical constituents of conventional cigarette smoke (CS) can disrupt this equilibrium by inducing the production of proinflammatory mediators and regulating intracellular inflammatory signaling pathways, thereby promoting oxidative stress [6]. There is evidence that conventional cigarettes produce significantly ($p < 0.05$) higher levels of particulate-phase radicals and gas-phase free radicals compared to HTPs [7]. Several studies, many of which were funded and conducted by HTP manufacturers, have examined biomarkers of exposure and potential harm, reporting that individuals who switch from conventional cigarettes to HTPs experience reduced exposure to tobacco smoke toxicants [8–21]. A systematic review of randomized controlled trials in which conventional cigarette smokers were randomized to switch to exclusive HTP use demonstrated that HTP users have lower exposure to toxicants and carcinogens than conventional cigarette smokers [22]. Furthermore, another systematic review evaluating differences in cardiovascular and respiratory biomarkers between HTP users and conventional cigarette smokers has reported improvements in clinically relevant risk factors, including soluble intercellular adhesion molecule type 1 (sICAM-1), 8-epi-prostaglandin F2α (8-epi-PGF2α), 11-dehydro-thromboxane B2 (11-DTX-B2), cholesterol concentration, high-density lipoprotein cholesterol (HDL-C) and forced expiratory volume in 1 s (FEV1) in HTP users compared to those who continued smoking conventional cigarettes [23]. However, despite the growing adoption of HTPs, even among individuals with chronic disease [24, 25], the extent to which these products confer a reduced health risk remains a subject of ongoing scientific debate [4].

The primary objective of this article is to provide an overview of available studies comparing the effects of HTPs and conventional cigarette smoking, with particular focus on chronic cardiovascular and respiratory diseases. A scoping review methodology has been adopted to address the aforementioned research question.

Methods

Search strategy

This scoping review was registered in the Open Science Framework (OSF), https://doi.org/10.17605/OSF.IO/6MG4Z. A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, and the Cochrane Library databases to identify relevant articles published in English between January 1, 2014, and March 31, 2025. The search strategy utilized the following terms: “heated tobacco products” OR “HTPs” OR “heat-not-burn” OR “HnB” OR “IQOS” OR “modified risk tobacco products” OR “tobacco heating system” OR “Tobacco heating device*” OR “Non-combusted tobacco” OR “Glo” OR “Ploom” OR “PAX” AND “cardiovascular diseases” OR “cardiovascular” OR “heart” OR “blood pressure” OR “atherosclerosis” OR “myocardial infarction” OR “arrhythmia” OR “heart failure” OR “stroke” OR “TIA*” OR “respiratory tract diseases” OR “lung diseases” OR “COPD” OR “asthma” OR “respiratory failure”.

Inclusion and exclusion criteria

The inclusion criteria comprised peer-reviewed studies published in English that compared the association between HTPs and conventional combustible cigarette use with cardiovascular and respiratory diseases. Both independently conducted studies and those sponsored by the tobacco industry were considered. Exclusion criteria included nonpeer-reviewed studies, conference abstracts, duplicate or irrelevant studies, surveys, publications in languages other than English, and studies conducted in vitro, ex vivo, or using animal models.

Data extraction

Two reviewers (MM and MP) independently screened the titles, abstracts, and full-text articles for eligibility. Any discrepancies in study selection were resolved through consensus, and, when necessary, in consultation with two additional reviewers (PA and GG). The reference lists of all included studies were also manually reviewed to identify any further relevant publications. For each study included in this scoping review, the following data were extracted: authors, year of publication, country, independence from industry, study design, population, and clinical outcomes related to cardiovascular and respiratory diseases.

Results

The PRISMA flow diagram (Fig. 1) illustrates the study selection process. The initial database search identified 1670 articles. After removing duplicates, 1107 articles remained for screening. Following the title and abstract screening and full-text assessment, 34 articles were identified as relevant and included in this scoping review.

Cardiovascular clinical outcomes

The characteristics of the included cardiovascular studies are summarized in Table 1. The association between HTPs and conventional cigarette use with cardiovascular outcomes

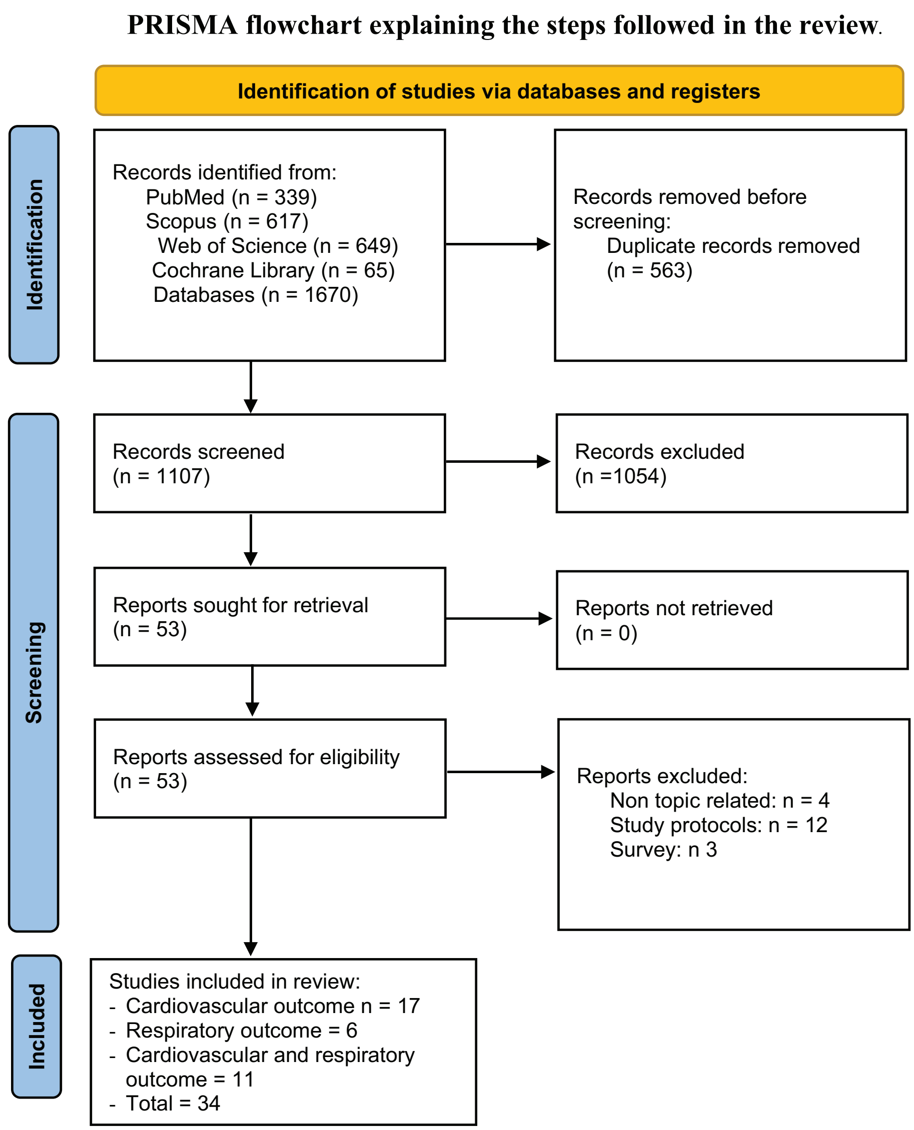


Fig. 1 PRISMA flowchart explaining the steps followed in the scoping review

Table 1 Characteristics of the included cardiovascular studies

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Lüdicke et al. https://doi.org/10.1093/ntr/ntx028 [30]	2018	Japan	Industry	Randomized controlled trial where 160 adult smokers were randomized to one of three groups: switch to menthol tobacco heating system (mTHS) 2.2, continue smoking menthol cigarettes, or smoking abstinence for 90 days	– Endothelial dysfunction – Oxidative stress – Platelet activation – Lipid metabolism – Metabolic syndrome – Inflammatory markers – Blood pressure	Switching to mTHS 2.2 significantly improved several potential harm biomarkers (BoPH) (soluble intracellular adhesion molecule-1, 8-epi-prostaglandin F2α, WBC count, high-density lipoprotein cholesterol) associated with CVD risk compared to continued menthol cigarettes smoking
Biondi-Zoccai et al. https://doi.org/10.1161/JAHA.118.010455 [36]	2019	Italy	Independent	Randomized crossover study of 20 healthy tobacco combustion cigarette (CC) smokers with 1 week wash out assigned to different cycles of new-generation HTP, electronic vaping cigarettes (EVC), and TC	– Oxidative stress – Antioxidant reserve – Endothelial dysfunction – Platelet activation – Blood pressure	HTP demonstrated significantly less impact on several biomarkers of oxidative stress and antioxidant reserve, including soluble Nox2-derived peptide ($p = 0.004$ and 0.001, respectively), 8-iso-prostaglandin F2α-III ($p = 0.004$ and < 0.001), and vitamin E ($p = 0.018$ and 0.044), when compared to both EVC and CC use. Furthermore, HTP and EVCs had similarly attenuated effects on FMD, hydrogen peroxide (H_2O_2) levels, H_2O_2-degrading activity, soluble CD40 ligand, and soluble P-selectin. The impact of HTP on blood pressure was less pronounced than that of TC ($p < 0.05$)
Lüdicke et al. https://doi.org/10.1158/1055-9965.EPI-18-0915 [28]	2019	United States	Industry	Randomized controlled trial of 984 adult smokers [496 continued smoking, 488 switched to THS 2.2 over 6 months	Changes in eight co-primary endpoints (HDL-C, WBC, sICAM-1, 11-DTX-B2, 8-epi-PGF2α)	Significant improvements ($p < 0.05$) were observed in five biomarkers (HDL-C, WBC) in smokers who switched to THS compared to those who continued smoking cigarettes
Haziza et al. https://doi.org/10.1093/ntr/ntz084 [31]	2020	United States	Industry	Randomized controlled trial where 160 healthy adult US smokers were randomized to one of three groups: switch to menthol THS 2.2, continue smoking menthol cigarettes, or smoking abstinence	– Endothelial dysfunction – Oxidative stress – Platelet activation – Lipid metabolism – Metabolic syndrome – Inflammatory markers – Blood pressure	Switching to mTHS 2.2 significantly ($p < 0.05$) reduced BoPH (sICAM-1, 8-epi-$PGF_2\alpha$) compared to continued menthol cigarettes smoking In normal weight subjects, more pronounced improvements in 11-$dTxB_2$, glucose

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Franzen et al. https://doi.org/10.1177/1358863X20943292 [43]	2021	Germany	Independent	Acute randomized crossover trial in 20 current smokers comparing the effects of using an HTP, a standard tobacco cigarette, e-cigarette with nicotine and e-cigarette without nicotine, each tested on separate occasions	– Heart rate – Blood pressure – Carotid–femoral pulse wave velocity	HTP, conventional tobacco cigarette, and e-cigarette with nicotine use was associated with an increase of systolic blood pressure, heart rate, and pulse wave velocity with conventional cigarettes showing a trend towards numerically more pronounced changes
Loffredo et al. https://doi.org/10.1136/thoraxjnl-2020-215900 [26]	2021	Italy	Independent	Observational, cross-sectional study comparing 60 individuals in three groups (20 chronic HTP users; 20 conventional combustion cigarette (CC) smokers; 20 nonsmokers)	– Endothelial dysfunction – Oxidative stress – Platelet activation	Both HTP and CC users exhibited adverse effects on endothelial function, increased oxidative stress, and heightened platelet activation, when compared with nonsmokers ($p < 0.05$)
Ioakeimidis et al. https://doi.org/10.1177/2047487320918365 [44]	2021	Greece	Independent	Acute randomized crossover trial in 22 current smokers comparing the effects of using an HTP for 5 min, a standard tobacco cigarette for 5 min, and a sham cigarette, each tested on separate occasions	– Heart rate – Blood pressure – Carotid–femoral pulse wave velocity	HTP use was associated with smaller numerical increases in arterial stiffness indices after smoking compared with conventional cigarettes; however, the differences between the smoking types were not statistically significant
Ikonomidis et al. https://doi.org/10.1038/s41598-021-91245-9 [46]	2021	Greece	Independent	Acute randomized, crossover trial followed by a chronic case control follow-up study. In the acute phase 50 current smokers randomized to consume a single conventional cigarette or HTP, then crossed over after 60 min to the alternate product. In the chronic arm: 50 smokers switched to HTP for 1 month and compared with a group of 25 ongoing conventional cigarette smokers	– Vascular function – Coronary flow reserve (CFR) – Arterial stiffness – Myocardial deformation – Myocardial work – Oxidative stress – Platelet activation	The acute use of HTP resulted in a significantly smaller rise in pulse wave velocity than CCs ($p < 0.05$) and did not affect other biomarker levels One month of HTP substitution resulted in favorable changes in several key parameters. These included reductions in flow-mediated dilation, enhanced CFR, increased total arterial compliance, improved global longitudinal strain, decreased wasted myocardial work, and lower levels of malondialdehyde and thromboxane B2 ($p < 0.05$). These findings suggest that HTP may be less harmful to cardiac and vascular function than traditional cigarettes

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Sakaguchi et al. https://doi.org/10.1093/ntr/ntab014 [32]	2021	Japan	Industry	Cross-sectional, post-marketing observational study of 459 adult Japanese participants categorized as exclusive users of a HTP or novel tobacco vapor (NTV), conventional cigarette smokers, and never-smokers	– Oxidative stress – Endothelial dysfunction – Platelet activation – Lipid metabolism	HTP users showed significantly better levels of several CVD-related biomarkers (HDL-cholesterol, triglyceride, sICAM-1, 11-DHTXB2, 2,3-d-TXB2, 8-epi-PGF2α, $p < 0.05$) compared to cigarette smokers, but levels were higher than in never-smokers
Yaman et al. https://doi.org/10.1016/j.taap.2021.115575 [45]	2021	Cyprus and Turkey	Independent	Prospective study of 27 healthy participants with chronic IQOS smoking history evaluated before smoking any tobacco product, after IQOS smoking, after cigarette smoking	– Cardiac function assessed transthoracic echocardiography and 2D speckle tracking – Heart rate – Blood pressure	Acute use of IQOS increases heart rate and impairs both systolic and diastolic myocardial function similar to conventional cigarette smoking ($p < 0.05$), but not blood pressure, which was increased significantly ($p < 0.05$) by conventional cigarettes only
Gale et al. https://doi.org/10.1007/s11739-021-02798-6 [18]	2021	United Kingdom	Industry	Randomized, controlled trial of healthy volunteer smokers assigned to one of three groups: continue smoking combustible cigarettes; switch to a tobacco heating product (THP); or abstain from smoking (smoking cessation) followed for 180 days	– Biomarkers of potential harm (BoPH) linked to CVD risk – Platelet activation – Oxidative stress – Inflammatory markers – Endothelial dysfunction – Lipid metabolism	Significant reduction ($p < 0.05$) of BoPH in a direction consistent with reduced harm (8-epi-prostaglandin F2α type III, white blood cell count) in THP users
Choi et al. https://doi.org/10.1161/CIRCULATIONAHA.121.054967 [50]	2021	South Korea	Independent	Nationwide cohort study of 5,159,538 adult men from the Korean National Health Insurance Service database	Incidence of cardiovascular disease assessed in relation to changes in smoking habits	Individuals who switched from traditional cigarettes to noncombustible nicotine or tobacco products had a lower risk of cardiovascular disease (aHR, 0.77 [95% CI, 0.65–0.91])
Benthien et al. https://doi.org/10.3390/medicines9040028 [38]	2022	Germany	Independent	A randomized acute exposure four arm cross over study involving 20 young adults who are occasional smokers or e-cigarette users, each participant exposed to 4 conditions: combustible cigarette, JUUL™e-cigarette, nicotine-free e-cigarette, and heated tobacco product, with > 48-h washout period between sessions	– Blood pressure – Arterial stiffness	Both JUUL™ and heated tobacco product exposure led to a significant increase in blood pressure, augmentation index adjusted for a heart rate of 75 bpm, and a decrease of reactive hyperemia index ($p < 0.05$), indicating acute vascular impairment

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Schirone et al. https://doi.org/10.3390/antiox11071237 [27]	2022	Italy	Independent	Observational, prospective, cross-sectional study comparing 60 individuals (27 males, 33 females). Subgroups by smoking status: nonsmokers, CC smokers, HTP smokers	– Endothelial dysfunction – Oxidative stress – Platelet activation	In the overall cohort, males vs females had no significant difference ($p > 0.05$) in FMD (%), NO, sNox2-dp, H_2O_2, sCD40L, sP-selectin, platelet aggregation, or cotinine levels. In this sample, although HTPs and CC smokers had impaired vascular/oxidative/platelet function compared to nonsmokers, when comparing male versus female within those groups, the differences between sexes for these markers were not statistically significant. HnBCs were associated with lower levels of sNox2-dp ($p = 0.026$) and sP-selectin ($p = 0.050$) compared to TCCs users
Gale et al. https://doi.org/10.1007/s11739-022-03062-1 [19]	2022	United Kingdom	Industry	Pseudo randomized, controlled, parallel-group study of adult smokers over 360 days (continued smoking, switch to HTP, or cessation)	– Biomarkers of potential harm (BoPH) linked to CVD risk – Platelet activation – Oxidative stress – Inflammatory markers – Endothelial dysfunction – Lipid metabolism	Beneficial improvements in several CVD-related biomarkers (e.g. 8-epi-Prostaglandin F2a type III, white blood cell count) observed in THP switchers and quitters
Hu et al. https://doi.org/10.1038/s41598-022-22337-3 [47]	2022	Japan	Independent	Cross-sectional analysis of workers (12,268 in Study I + 36,503 in Study II; pooled total 48,771) from multiple companies participating in health check-ups, categorized by tobacco product use (never, past, exclusive HTP, dual users, exclusive cigarette)	Circulating high-density lipoprotein cholesterol (HDL-C) concentrations, odds ratio (OR) of low HDL-C (< 40 mg/dL for men; < 50 mg/dL for women)	Exclusive HTP users had slightly but significantly lower HDL cholesterol levels compared with never smokers (pooled mean difference −1.1 [95% CI −1.5 to −0.6] mg/dL), while exclusive cigarette smokers exhibited a larger reduction (−4.3 [−4.7 to −3.9] mg/dL). Exclusive HTP users also had an increased likelihood of low HDL-C compared with never smokers (pooled OR, 1.25 [95% CI, 1.09–1.43]), although this risk was lower than that observed in exclusive cigarette smokers (OR, 2.09 [95% CI, 1.88–2.32])

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Belkin et al. https://doi.org/10.3390/ijms24119432 [35]	2023	Germany	Independent	A randomized, four-arm semi-blind pilot study with a crossover study design of 40 young active smoke Rs studied in two different approaches during and after consuming HTPs, combustible cigarettes, JUUL, and e-cigarettes (with/without nicotine)	– Inflammatory markers – Endothelial dysfunction – Arterial stiffness	HTPs increased inflammatory markers and proinflammatory cytokines and arterial stiffness ($p < 0.05$) like combustible cigarettes
Majek et al. https://doi.org/10.1183/23120541.00595-2022 [41]	2023	Poland	Independent	Acute exposure study with a cross-sectional group comparison design of 160 healthy young adults (40 heated tobacco users, 40 conventional cigarette smokers, 40 e-cigarette users, 40 nonsmokers)	– Blood pressure – Heart rate	Acute use of heated tobacco products caused increases blood pressure and heart rate, in a similar direction as in conventional cigarettes and e-cigarettes groups
Goebel et al. https://doi.org/10.3390/toxics11090758 [40]	2023	Germany	Independent	A five-arm crossover study conducted in 17 healthy occasional smokers to compare a combustible cigarette, a nicotine-free e-cigarette, two heated tobacco products ("IQOS" and "GLO"), and a sham condition (vaping with an e-cigarette without liquid)	– Hemodynamic parameters – Arterial stiffness	All products containing nicotine (combustible cigarettes, heated tobacco products) exhibit similar acute physiological effects, showing significant comparable alterations in heart rate, blood pressure, and arterial stiffness
Picchio et al. https://doi.org/10.1111/eci.14140 [33]	2024	Italy	Independent	Observational, prospective, cross-sectional study comparing 60 healthy individuals in three groups (20 chronic HTP; 20 traditional combustion cigarette (CC) smokers; 20 nonsmokers)	– Profiling of circulating micro-RNAs – (miRNAs) associated with chronic diseases, including cardiovascular disease	72 miRNAs were exclusively expressed in CC users, 10 miRNAs exclusively in HTP users, and 26 miRNAs were shared between the two smoking groups.
Ansari et al. https://doi.org/10.1080/1354750X.2024.2358318 [29]	2024	United States	Industry	Randomized controlled trial (with extension) in adult smokers (initial $n = 984$; 672 entering 6-month extension) divided into groups: predominantly HTP users, dual users, current smokers	Changes in biomarkers of potential harm (BoPHs) that are mechanistically linked to cardiovascular risk (oxidative stress, inflammation, endothelial dysfunction, platelet activation, lipid metabolism)	At 12 months, participants who switched predominantly to the HTP had more favorable biomarker profiles compared to continued cigarette smokers

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Hu et al. https://doi.org/10.1093/ije/dyae114 [48]	2024	Japan	Independent	Prospective cohort study of 30,152 workers initially free of hypertension, followed over 2.6 years	Incident hypertension assessed via annual health checkups	Compared to never smokers, exclusive cigarette smokers had HR = 1.26 (95% CI, 1.13–1.41), exclusive HTP users had HR = 1.19 (95% CI, 1.06–1.34), and dual users had HR = 1.16 (95% CI, 0.98–1.38) for development of hypertension
Jung et al. https://doi.org/10.1177/1179173X241271551 [42]	2024	Germany	Independent	Four-arm intervention study with a crossover design 20 healthy subjects examining cigarette smoking, vaping IQOS, or vaping e-cigarettes (with or without nicotine)	– Hemodynamic parameters – Arterial stiffness	All products with or without nicotine (combustible cigarettes, heated tobacco products) exhibit similar acute physiological effects, showing significant comparable alterations in heart rate, blood pressure, and arterial stiffness ($p < 0.05$)
Harada et al. 10.2188/jea.JE20230170 [34]	2024	Japan	Independent	Observational, prospective, cross-sectional study of 9922 participants; Follow-up subset: 3334 participants	Plasma metabolite profiles (glutamate metabolism pathway, which has been implicated in the development of cardiovascular disease)	HTPs who had switched from conventional cigarettes exhibited a metabolite profile more similar to that of cigarette smokers than nonsmokers ($p < 0.05$)
Jee et al. https://doi.org/10.18332/tid/194490 [49]	2024	South Korea	Independent	Prospective cohort study of 178,004 participants	Effect of heated tobacco product use on metabolic syndrome, a known CVD risk factor	Current HTP use has been associated with an increased risk of developing metabolic syndrome (HR = 1.68 [95% CI 1.25–2.26]). compared to never users
Ansari et al. https://doi.org/10.1080/1354750X.2025.2461069 [21]	2025	Asia, Europe	Industry	Cross-sectional observational study, healthy participants ($n = 982$) divided into groups: current smokers, voluntary HTP users (≥ 2 years), former smokers	Changes in biomarkers of potential harm (BoPHs) that cover pathways implicated in cardiovascular risk (oxidative stress, inflammation, endothelial dysfunction, platelet activation, lipid metabolism)	Compared to current smokers, HTP users showed significantly favorable differences ($p < 0.05$) in all BoPH measured
Kim et al. https://doi.org/10.1016/j.etap.2025.104657 [37]	2025	Republic of Korea	Independent	Preliminary, observational exposure study; 10 participants (smokers and nonsmokers) exposed to first- and second-hand smoke from HTP and conventional cigarettes	Heart rate variability (HRV)	Conventional cigarettes and HTP were shown to affect heart rate variability at a similar extent and differently from nonsmokers, however these findings were preliminar and obtained in a small sample size

Table 1 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main cardiovascular outcomes	Main results
Ahmed et al. https://doi.org/10.4081/monaldi.2025.3316 [39]	2025	Egypt	Independent	Prospective observational study of 91 participants (46 current cigarette smokers divided into 2 smoking groups, plus 45 healthy nonsmokers)	Heart rate (HR)	Smoking heated tobacco or traditional cigarettes produced increases in HR ($p<0.05$)

was examined in 8 industry-dependent and 20 independent studies.

A cross-sectional observational study compared endothelial function, oxidative stress, and platelet activation in 20 chronic users of HTPs, 20 chronic smokers of conventional combustion cigarettes (CCs), and 20 nonsmokers. The results showed that the use of HTPs and CCs was associated with increased oxidative stress, endothelial dysfunction, and platelet activation [26]. However, this study has several limitations, including a small sample size, lack of randomization, and the performance of multiple statistical tests, which may increase the risk of a Type I error. In addition, CC smokers were younger and had a lower pack-year smoking history compared to HTP users, who may have recently switched to HTPs. This difference could mask the actual differences between the two groups in terms of endothelial function, oxidative stress, and platelet activation [26].

In a study assessing the impact of HTPs by sex, no statistically significant differences were found between males and females for biomarkers such as nitric oxide (NO), hydrogen peroxide (H2O2), soluble CD40 ligand (sCD40L), soluble Nox2-derived peptide (sNox2-dp), soluble P-selectin (sP-selectin), platelet aggregation, cotinine levels, or flow-mediated dilation (FMD). Although several biomarkers showed similar levels between HTPs and conventional cigarettes, HTPs were associated with lower levels of sNox2-dp (−5.3 ng/mL, $p=0.026$) and sP-selectin (−1.5 ng/mL, $p=0.050$) [27].

Another study involving 984 adult smokers in the US assessed changes in eight co-primary endpoints, including HDL-C, white blood cell (WBC) total count, soluble intercellular adhesion molecule-1 (sICAM-1), urinary 11-dehydrothromboxane B2 (11-DTX-B2), urinary 8-epi-prostaglandin F2 alpha (8-epi-PGF2α), urinary total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL). Participants were randomized to either continue smoking their preferred cigarette brand ($n=496$) or switch to using HTP ($n=488$) for 6 months. Significant improvements were observed in those who switched to HTP compared with those who continued smoking cigarettes, including an increase in HDL-C (+3.09 mg/dL, $p<0.001$), reduced WBC count (−0.420 G/L, $p<0.001$), reduced endothelial dysfunction (−2.86% sICAM-1, $p<0.030$), lower oxidative stress (−6.8% 8-epi-PGF2α, $p<0.018$), and reduced exposure to carcinogens (−43.5% Total NNAL, $p<0.001$). These findings suggest a potential reduction in disease risk for individuals who transition from conventional cigarettes to HTP [28]. A 6-month extension of this study confirmed the trend toward favorable changes in multiple risk biomarkers among participants predominantly using HTP [29].

Two studies, one conducted in adult US smokers and the other in adult Japanese smokers, investigated changes in relevant risk markers among participants who switched to mentholated HTP (mHTP) 2.2 compared to those who continued smoking menthol cigarettes [30, 31]. In the study involving adult US smokers, 80 subjects were randomized to the m HTP group and 41 to the menthol cigarette (mCC) group, and were followed for 90 days. Switching to m HTP was associated with a significant reduction in sICAM-1 (−11%, $p < 0.05$) and 8-epi-PGF2α (−13%, $p < 0.05$) when compared with participants who continued smoking menthol cigarettes [31]. In the study involving adult Japanese smokers, 78 subjects were randomized to the mHTP group and 42 to the mCC group, and were also followed for 90 days. Switching to mHTP was associated with a significant reduction in sICAM-1 (−8.7%, $p = 0.012$), 8-epi-PGF2α (−13%, $p = 0.016$), and WBC count (−0.57 G/L, $p = 0.017$), as well as an increase in HDL cholesterol (+4.5 mg/dL, $p = 0.008$), compared with participants who continued smoking menthol cigarettes [30]. In an observational cross-sectional study comparing exclusive HTP users ($n = 259$) with conventional cigarette smokers ($n = 100$), adult HTP users showed significantly lower blood levels of triglycerides, sICAM-1, and WBC count (−22.8%, −12.4%, and −17.8%, respectively), and higher levels of HDL-C (+13.9%) compared to cigarette smokers. Similarly, urinary levels of 11-DHTXB2, 2,3-d-TXB2, and 8-epi-PGF2α were significantly lower in the HTP group (−24.5%, −34.4%, and −21.6%, respectively) compared to the cigarette smoker group [32]. Another study investigating changes in biomarkers of potential harm (BoPH) in smokers who switched from conventional cigarettes to the exclusive use of HTP ($n = 127$) over 180 and 360 days found a significant reduction in 8-epi-prostaglandin $F_2\alpha$ type III (−31% at 360 days) and in WBC count (−18% at 360 days) among those who switched to HTP compared with smokers who continued using conventional cigarettes ($n = 59$) [18, 19]. In a cross-sectional study comparing adults who smoked conventional cigarettes ($n = 296$) with those who had voluntarily switched to exclusive HTP use for more than 2 years, HTP use was associated with lower levels of 8-epi-PGF2α (−23.6%, $p < 0.001$), sICAM-1 (−11.8%, $p < 0.001$), 11-dehydrothromboxane B2 (11-DTX-B2) (−30.4%, $p < 0.001$), and WBC count (-0.694×10^9 cells/L, $p < 0.001$), as well as higher HDL cholesterol (+0.094 mmol/L, $p = 0.002$), as compared to the current conventional cigarette smokers [21].

Circulating microRNAs (miRNAs) are key molecular mediators in pathogenic mechanisms and potential biomarkers for personalized risk assessment. A recent study aimed at identifying the circulating miRNA profile in chronic users of HTP, chronic smokers of conventional cigarettes, and nonsmokers found a differential expression of miRNAs associated with chronic diseases, including cardiovascular disease. Specifically, 72 miRNAs were exclusively expressed in conventional cigarette users, 10 miRNAs exclusively in HTP users, and 26 miRNAs were shared between the two smoking groups. These findings suggest that the circulating miRNA profile in HTP users is intermediate between that of nonsmokers and conventional cigarette smokers, indicating a potentially reduced—yet not absent—biological impact [33]. Another study investigating metabolomic profile changes found that users of HTPs who had switched from conventional cigarettes exhibited a metabolite profile more similar to that of cigarette smokers than nonsmokers. These changes included alterations in the glutamate metabolism pathway, which has been implicated in the development of cardiovascular disease. These results suggest that even after switching to HTPs, some metabolic effects of prior cigarette smoking—particularly those involving glutamate metabolism—may persist [34]. Furthermore, another study showed that HTPs increased inflammatory markers and pro-inflammatory cytokines, similar to those found in conventional cigarettes, which correlated with clinical measures of arterial stiffness [35].

A randomized crossover study conducted among 20 conventional cigarette smokers aimed to compare the effects of HTPs, electronic vaping cigarettes (EVCs), and conventional cigarettes on oxidative stress, antioxidant reserve, flow-mediated dilation (FMD), platelet function, and blood pressure [36]. Compared with conventional cigarette smoking, HTP use was associated with significantly lower levels of soluble Nox2-derived peptide ($p = 0.004$), soluble P-selectin ($p < 0.001$), 8-iso-prostaglandin $F_2\alpha$-III ($p < 0.001$), vitamin E ($p = 0.044$), hydrogen peroxide (H_2O_2) ($p = 0.042$), and systolic blood pressure ($p = 0.002$), as well as a smaller reduction in FMD ($p = 0.048$) [36].

Studies investigating the acute effects of HTPs and conventional cigarette smoking on heart rate, arterial blood pressure, and arterial stiffness have produced inconsistent results. Some have reported that conventional cigarette smokers and HTP users exhibit similar acute increases in heart rate, arterial blood pressure, and arterial stiffness [37–42]. In contrast, others have observed either no change or numerically smaller, but not statistically significant, increases in arterial stiffness among HTP users compared with conventional cigarette smokers [43, 44].

However, in this context, the observed hemodynamic effects are primarily attributable to the well-known transient action of nicotine during acute exposure. Therefore, the design of these studies may not be entirely appropriate for evaluating clinically meaningful changes in arterial stiffness, due to the limited duration of exposure to combustion-related toxicants. Additionally, other studies have shown that, similar to conventional cigarette smoking, acute use of HTPs impairs both systolic and diastolic myocardial function [45].

A study comparing the effects of HTPs and conventional cigarette smoking on coronary flow and myocardial and vascular function found that one month of HTP substitution resulted in favorable changes in several key parameters. These included reductions in carbon monoxide (CO) levels, flow-mediated dilation, enhanced coronary flow reserve (CFR), increased total arterial compliance, improved global longitudinal strain, decreased wasted myocardial work, and lower levels of malondialdehyde and thromboxane B2. These findings suggest that HTPs may be less harmful to cardiac and vascular function than conventional cigarettes [46].

A pooled analysis from the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) study, including 48,771 workers, found that exclusive HTP users had slightly but significantly lower HDL cholesterol levels compared with never smokers (pooled mean difference −1.1 [95% CI −1.5 to −0.6] mg/dL), while exclusive cigarette smokers exhibited a larger reduction (−4.3 [−4.7 to −3.9] mg/dL). Exclusive HTP users also had an increased likelihood of low HDL-C when compared with never smokers (pooled OR, 1.25 [95% CI, 1.09–1.43]), although this risk was lower than that observed in exclusive cigarette smokers (OR, 2.09 [95% CI, 1.88–2.32]) [47].

A 2.6-year prospective cohort study involving 30,152 workers participating in the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study reported a similar risk of developing hypertension among exclusive conventional cigarette smokers (HR 1.20, 95% CI 1.08–1.34) and exclusive heated tobacco product (HTP) users (HR 1.26, 95% CI 1.13–1.42) compared with never smokers [48]. In addition, HTP use was associated with an increased risk of developing metabolic syndrome (adjusted HR 1.68, 95% CI 1.25–2.26) compared with never users [49]. However, further studies are needed to confirm these findings, particularly given that the study relied on self-reported tobacco use data, which may be subject to reporting bias [49].

A population-based study involving 5,159,538 adult men from the Korean National Health Insurance Service database found that individuals who switched from conventional cigarettes to noncombustible nicotine or tobacco products (NNTPs) had a lower risk of cardiovascular disease (adjusted HR, 0.77 [95% CI 0.65–0.91]) compared to those who continued smoking conventional cigarettes. However, individuals who stopped smoking conventional cigarettes but continued using noncombustible nicotine or tobacco products showed a higher cardiovascular risk compared with long-term (≥ 5 years) combustible cigarette quitters who did not use NNTPs (adjusted HR, 1.23 [95% CI 1.04–1.45]) [50].

Respiratory clinical outcomes

The characteristics of the included pulmonary studies are summarized in Table 2. The association between the use of HTPs and conventional cigarettes with respiratory outcomes was examined in 7 industry-sponsored and 10 independent studies.

A clinical investigation comparing current cigarette smokers, former smokers, never smokers, e-cigarette users, and HTP users assessed mucociliary clearance using the saccharin transit time test (MCCTT). The results showed that former smokers who had switched to exclusive HTP use exhibited a shorter MCCTT (median 8.00 min) compared with current smokers (median 13.15 min), and values comparable to those of never smokers (median 7.24 min) and former smokers (median 7.26 min), suggesting recovery of mucociliary function [51]. In a study involving adult US smokers, 80 participants were randomized to the menthol tobacco heating system (mTHS) group and 41 to the menthol conventional cigarette (mCC) group and were followed for 90 days. Switching to mTHS was not associated with significant changes in percent predicted forced expiratory volume in one second (FEV_1% pred) compared with participants who continued smoking menthol cigarettes [31]. Similarly, acute exposure to HTPs did not result in any significant change in FEV_1% predicted values among a group of 40 HTP users compared with 40 conventional cigarette smokers [41]. In a study conducted in the United Kingdom, 79 current cigarette smokers and 197 former smokers who had switched to HTP use were followed for 180 and 360 days. HTP users exhibited higher FEV_1% pred values (91.9% at baseline, 93.0% at 180 days, and 92.1% at 360 days, respectively) compared with cigarette smokers (91.5% at baseline, 88.1% at 180 days, and 86.2% at 360 days, respectively) [18, 19]. Similarly, in another previously reported study, smokers who transitioned from conventional cigarettes to HTPs demonstrated significant improvements in post-bronchodilator FEV_1% pred (+ 1.28, $p = 0.008$) and reductions in carboxyhemoglobin (COHb) levels (–32.2%, $p < 0.001$) compared with individuals who continued smoking conventional cigarettes [28]. These results were confirmed during a six-month extension period, although the statistical significance of the differences in FEV_1% pred was not maintained [29]. In another previously mentioned cross-sectional study conducted under real-world conditions with participants followed for at least two years, former smokers who had switched to tobacco heating system (THS) use exhibited higher FEV_1% predicted values (+ 2.983%, $p = 0.002$) compared with current conventional cigarette smokers [21]. In the above observational cross-sectional study, exclusive HTP use was associated with significantly higher FEV_1 levels (+ 4.1%, $p = 0.035$) compared with conventional cigarette smoking [32]. A study conducted among 46 current conventional cigarette smokers compared the acute effects of HTPs on exhaled carbon monoxide (CO) levels and pulmonary function. One group of 23 participants smoked their usual cigarette brand, while the other 23 participants used an HTP stick. In both groups, parameters were assessed before

Table 2 Characteristics of the included pulmonary studies

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Ludicke et al. https://doi.org/10.1158/1055-9965.EPI-18-0915 [28]	2019	U.S	Industry	Randomized, controlled, 2-arm parallel group, multicenter, open-label, ambulatory trial Adult smokers ($n \approx 984$) in the U.S. were randomized to either continue smoking their usual cigarettes ($n \approx 496$) or switch to a heat-not-burn (HNB) product: the IQOS/Tobacco Heating System 2.2 (THS) ($n \approx 488$) for 6 months	Analysis of 8 biomarkers of effect (BoEfx) and Biomarkers of exposure (BoExp)	The % predicted FEV_1 improved in the THS group relative to the cigarette-continuing group The reduction in COHb and nitrosamine biomarker (Total NNAL) implies reduced inhalation of harmful combustion by-products that contribute to lung injury, COPD progression, and lung cancer
Beatrice et al. https://doi.org/10.3390/ijerph16203916 [52]	2019	Italy	Independent	Observational switching intervention (nonrandomized) in smokers resistant to cessation, with measurement at baseline and after six months 40 male smokers who were unwilling or unable to quit cigarettes Participants were offered a full switch to either electronic cigarettes (e-Cigs) ($n = 20$) or a tobacco heating system (THS) ($n = 20$) for six months	Nicotine addiction score and exhaled carbon monoxide (eCO) levels at baseline and after 6 months	In the e-Cig group: median %COHb dropped by −1.6 (Q1–Q3: −2.24; −1.28) and ppm dropped by −10 (Q1–Q3: −10; −8).In the THS group: median % COHb dropped by −1.28 (Q1–Q3: −1.92; −1.12) and ppm dropped by -8 (Q1–Q3: −12; −7). In both groups switching produced eCO levels "within the range of nonsmoker status". The THS group had a significantly lower reduction in ppm CO compared to the e-Cig group ($p < 0.05$)
Haziza et al. https://doi.org/10.1093/ntr/ntz084 [31]	2020	US	Industry	Randomized, three-arm parallel-group clinical study in 160 healthy adult US smokers who smoked menthol cigarettes Participants were randomized (2:1:1) to: - Switch to the menthol version of the IQOS "Menthol Tobacco Heating System 2.2" (mTHS) - Continue menthol cigarettes (mCC) - Abstain from smoking (SA) Study period: 5 days in confinement followed by 86 days ambulatory (=3 months)	Endpoints: Biomarkers of potential harm (BOPHs) spanning oxidative stress, endothelial dysfunction, lipid metabolism, inflammation—and one lung-function marker	No statistically significant differences in FEV_1%pred were found across the three groups (mTHS, mCC, SA) at three months In the exploratory subgroup of normal-weight subjects, some favorable changes including FEV_1%pred were mentioned as having occurred in the mTHS group compared with mCC

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Sharman et al. 10.12974/2312-5470.2021.07.05 [54]	2021	Kazakhstan	Independent	Prospective cohort study 1200 participants aged 40–59 with at least 10 pack-year history of combustible cigarette (CC) smoking Participants were grouped as continuing combustible cigarette users (CC group) versus users of heated tobacco products (HTP group). The study followed them for 2 years	(1) Patient-reported CAT scores; (2) Post-bronchodilator lung function parameters, including FEV1 and FVC; (3) Exercise tolerance using 6MWD Test; (4) MetS components, including waist circumference, fasting glucose, blood lipids, and blood pressure	Post-bronchodilator FEV1 and FVC Decreased over time for both CC and HTP users. FVC for HTP users was significantly lower compared to CC users while over time their lung function improved and became significantly better compared to CC users HTP smoking was significantly associated with lower CAT scores for 24-month follow-up compared to CC smokers
Sakaguchi et al. https://doi.org/10.1093/ntr/ntab014 [32]	2021	Japan	Industry	Observational, cross-sectional, three-group, and multi-center study conducted between April 2019 and September 2019. 459 participants were recruited and divided into 3 groups - NTV novel tobacco vapor group ($n=259$); - CC conventional cigarette group ($n=100$); NS never smokers group ($n=100$)	Comparison of levels of established biomarkers of potential harm (BoPH) among (1) Exclusive heat-not-burn (HNB) product users, (2) Exclusive cigarette smokers, and (3) Never-smokers under real-world (post-marketing) conditions	Despite favorable shifts in multiple biomarkers of potential harm among HNB users, pulmonary function indices (FEV_1, FVC, and FEV_1/FVC) in exclusive HNB users did not significantly differ from those in current cigarette smokers, whereas never-smokers demonstrated higher spirometric values
Gale et al. https://doi.org/10.1007/s11739-021-02798-6 [18]	2021	UK	Industry	Randomized controlled trial Duration: Baseline → Day 180 Smoking categories - Group A ($n=59$): Continue smoking combustible cigarettes - Group B ($n=127$): Switch to exclusive THP use - Group D ($n=109$): Abstain from cigarette smoking - Group E ($n=37$): Never smokers	Determination of whether adult smokers switching from conventional combustible cigarettes to exclusive use of a tobacco-heating product (THP) show changes over 180 days in biomarkers of exposure (BoE) and biomarkers of potential harm (BoPH) linked to disease risk (oxidative stress, cardiovascular, respiratory and cancer-related pathways)	Fractional exhaled nitric oxide (FeNO) increased in the THP-switch group over 180 days but was stable in the continue-smoking group. Higher FeNO is interpreted as reduced smoking-induced airway oxidative stress/inflammation

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Polosa et al. https://doi.org/10.1177/20406223211035267 [51]	2021	Italy	Independent	Cross-sectional study designed to compare five study populations: (1) 39 current smokers; (2) 40 former smokers; (3) 40 never smokers; (4) 20 exclusive e-cigarettes (ECs) users (former smokers); and (5) 20 exclusive HTP users (former smokers)	Mucociliary clearance by measuring saccharin test transit time (MCCTT)	Current smokers had a median (IQR) MCCTT of 13.15 (9.89–16.08) min, which was significantly longer compared with that of never smokers at 7.24 (5.73–8.73) min, former smokers at 7.26 (6.18–9.17) min, exclusive EC users at 7.00 (6.38–9.00) min, and exclusive HTP users at 8.00 (6.00–8.00) min
Polosa et al. https://doi.org/10.1007/s11739-021-02674-3 [55]	2021	Italy	Independent	Retrospective study, conducted from September 2013 to December 2015 in the outpatient clinics setting in four Italian hospitals 38 Chronic Obstructive Pulmonary Disease (COPD) patients divided in two groups age- and sex-matched: - 19 COPD HTP users (COPD patients who reduced or ceased cigarette consumption by switching to HTPs); 19 COPD cigarette smokers (control group)	Evaluation of the long-term health impact (over 3 years) of switching from conventional cigarettes to heated tobacco products (HTPs) in patients with COPD	For COPD patients who switched to HTPs (or reduced smoking via HTPs), the study observed clinically meaningful and sustained improvements in exacerbation rate, symptom burden (CAT), and exercise capacity (6MWD) over 3 years These health gains occurred despite the lack of improvement in spirometric lung-function indices (which is common in COPD with established airway damage)

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Majek et al. https://doi.org/10.1183/23120541.00595-2022 [41]	2022	Poland	Independent	Laboratory-based intervention study. 160 healthy young adults were assigned to one of four groups according to their self-reported smoking status: - Exclusive traditional cigarette smokers (T group, $n=40$), - Exclusive heated tobacco users (H group, $n=40$) - Exclusive users of e-cigarettes (E group, $n=40$) nonsmokers, defined as never-smokers (C group (control), $n=40$)	Examine the acute health effects on the respiratory and cardiovascular systems during the use of HTPs as well as to compare these effects with acute health effects evoked by cigarette smoking or the use of electronic cigarettes (e-cigarettes) heart rate, blood pressure, oxygen saturation, exhaled carbon monoxide (CO), fractional exhaled nitric oxide (FeNO), temperature of exhaled air, and spirometry (pulmonary-function test) were measured immediately after exposure and again at 30 min	FeNO: after 5 min of exposure, there was a statistically significant decrease in FeNO in the HTP (H) group Exhaled CO: Only the cigarette smokers (T group) showed a statistically significant increase in exhaled CO levels. The HTP and E-cigarette groups did not show a notable rise in CO in this acute testing. Temperature of exhaled air: A slight but statistically significant increase in exhaled-air temperature after 30 min was seen in the cigarette (T) and e-cigarette (E) groups, though the change in HTP group was not highlighted. Elevated exhaled temperature might reflect airway heating/inflammation
Gale et al. https://doi.org/10.1007/s11739-022-03062-1 [19]	2022	UK	Industry	Prospective, ambulatory cohort study in adult healthy smokers Participants were allocated into four groups: - Continue smoking conventional cigarettes - Switch completely to a specific tobacco-heating product (THP) - Quit all tobacco/nicotine use Never smokers	Analysis of biomarkers of exposure (BoE) and biomarkers of potential harm (BoPH) – the latter including measures relevant to oxidative stress, inflammation, vascular/respiratory disease risk	For the "switch to THP" group, FeNO increased by ~ 38% between baseline and day 360, bringing it closer to never-smoker levels For the cessation group, FeNO increased ~ 91% over the same period In the "switch to THP" group, % predicted FEV_1 at day 360 was essentially stable over the year In the "cessation" group, % predicted FEV_1 was also essentially stable

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Goebel et al. https://doi.org/10.3390/toxics11090758 [40]	2023	Germany	Independent	Single-center, five-arm crossover study 17 healthy occasional smokers. Smoking categories: (a) Combustible cigarette (Cig) (b) e-cigarette without nicotine (E-Cig (-) (c) Heated tobacco product "IQOS", (d) Heated tobacco product "GLO", sham smoking, vaping with an e-cigarette without liquid	Acute effects on arterial stiffness and small airway function in two heated tobacco products (IQOS and GLO) and compared them to combustible cigarettes, e-cigarettes without nicotine, and sham smoking	Airwave oscillometry (AOS) of the lung showed impaired resistance and reactance immediately after the consumption of all devices except sham smoking. Resistance was increased at 5 Hz, a sign of central obstruction, and at 5–19 Hz, reflecting peripheral obstruction probably caused by acute bronchoconstriction. The increased area of reactance reflects impaired lung elasticity and is a marker for a small airway disease
Odani et al. 10.1136/ bmjresp-2023-001793 [53]	2024	Japan	Independent	Single-centre observational cross-sectional study From 1 December 2021 through 30 September 2022, 3080 patients scheduled for who attended a preoperative assessment. 2850 patients included in the analysis Smoking categories: - Never users - Former HTP- only users - Former cigarette- only users - Former dual, current HTP- only users - Current cigarette- only users - Current dual users	Association between HTP use and airway obstruction (FEV1/FVC < 0.7)	Exclusive HTP users ($n = 92$) showed a lower prevalence of airway obstruction defined as the ratio of FEV1 to forced vital capacity (FVC) less than the lower limit of normal compared to current conventional cigarette ($n = 266$) (21.7% vs. 29.7%, respectively). Airway obstruction was more likely present in current conventional cigarette smokers (adjusted prevalence ratio-APR 2.57 95%CI 2.01–3.28) than in exclusive HTP users (APR 2.32 95%CI 1.54–3.49)
Jung et al. https://doi.org/10.1177/1179173X241271551 [42]	2024	Germany	Independent	Single-center, four-arm intervention study in a cross overdesign. 20 healthy subjects (10 male and 10 female), all at least occasional smokers Each subject completed four conditions: 1) Conventional cigarette smoking 2) Use of a heated tobacco product (HTP; specifically, IQOS) 3) E-cigarette with nicotine 4) E-cigarette without nicotine	Analysis of the earliest changes in small airway function and immediate effects on hemodynamics after using e-cigarettes, HTPs and combustible cigarettes	After using nicotine-containing products - Significant increase in central airway resistance and peripheral airway resistance - Significant increase in airway reactance indicating altered small-airway mechanics - Tidal volume (TV) also rose significantly after nicotine-containing product use In contrast, the nicotine-free e-cigarette arm did not produce statistically significant changes in these small airway parameters

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Ansari et al. https://doi.org/10.1080/1354750X.2024.2358318 [29]	2024	US	Industry	Randomized controlled trial in adult smokers with a 6-month extension. Participants were randomized to either continue smoking conventional cigarettes or switch to the Tobacco Heating System 2.2 (THS) (nonmentholated). Follow-up for biomarker assessment at baseline, 3, 6, and 12 months - PredTHS use (defined as $\geq$ 70% of daily tobacco stick use (THS use) on average (on at least 50% of the days over 12 months) - Dual use (defined as 1% to < 70% THS use. cigarette smoking(cig) was defined as < 1% THS use - 'Other' use group: all participants who did not meet previous criteria	Analysis of biomarkers of potential harm (BoPHs) related to pathophysiological pathways implicated in smoking-related diseases	FeV1%pred values were slightly higher in the predTHS group across the study, starting from 3 months The proportion of participants who reported a regular need to cough was lower in the predTHS group than in the cig group
Nikolina et al. https://doi.org/10.3390/diseases12070144 [62]	2024	Serbia	Independent	Cross-sectional observational study 74 Ulcerative Colitis (UC).patients, 78 Chronic Obstructive Pulmonary Disease (COPD) patients, and 33 Diabetes Mellitus (DM) patients 3 groups within each disease category: (a) Patients using CCs, (b) Patients using HTPs, (c) Nonsmoking ("air") controls	Evaluation of the use of conventional combustible cigarettes (CCs) versus heated-tobacco products (HTPs) in influencing systemic inflammatory responses in patients with chronic inflammatory diseases: COPD, DM and UC	The study suggests HTPs may modulate the inflammatory environment in COPD differently from CCs (less pro-inflammatory but more immunosuppressive/profibrotic), which could influence lung function/airway health over time
Ansari et al. https://doi.org/10.1080/1354750X.2025.2461069 [21]	2025	Asia and Europe	Industry	Cross-sectional observational study of healthy adult participants ($n = 982$) between June 2022 and December 2023 divided into three groups: - Current smokers (combustible cigarettes) - Users who had voluntarily switched to a tobacco heating system (THS) for $\geq$ 2 years - Former smokers who had quit	Analysis of biomarkers of potential harm (BoPH) associated with pathways of smoking-related disease: including % predicted post-bronchodilator FEV_1	Favorable differences in the BoPH endpoints including the lung-function measure (% predicted FEV_1) compared to current smokers of combustible cigarettes The THS users' results for % predicted FEV_1 were similar to those of former smokers (quitters) rather than current cigarette smokers

Table 2 (continued)

Authors	Year of publication	Country	Sponsor	Study design and population	Main pulmonary outcomes	Main results
Ahmed et al. 10.4081/monaldi.2025.3316 [39]	2025	Egypt	Independent	Prospective observational analytical study 91 participants were randomized into 3 smoking categories: - Group 1: 23 subjects of current cigarette smokers. No smoke for a minimum 12 h before the study assessment of one normal cigarette - Group 2: 23 subjects of current cigarette smokers. No smoke for a minimum 12 h before the study assessment of one IQOS tobacco stick Group 3: control group of 45 normal healthy subjects with no history of any type of smoking	1) Exhaled carbon monoxide (CO) 2) Serum cotinine (nicotine exposure) 3) Oxygen saturation and pulmonary parameters (PFR)	HTPs have acute respiratory effects like conventional cigarettes (CCs) but with less exhaled CO than CCs, although these changes were relatively minor and not likely to be of major clinical significance

smoking and five minutes after smoking either the heated tobacco product or the conventional cigarette, according to the study protocol. Exhaled CO levels were significantly higher after conventional cigarette smoking than after HTP use ($p < 0.001$). No significant changes were observed in spirometric parameters, while oxygen saturation (SpO_2) was modestly reduced in both groups. However, it is important to note that the two groups showed significant differences in pre-smoking spirometry measurements, making the results difficult to interpret [39].

A longitudinal study involving 40 smokers who were unwilling or unable to quit evaluated the impact of switching to electronic cigarettes (e-cigarettes) or THS over six months. Both groups, each comprising 20 participants, showed a significant reduction in exhaled carbon monoxide (eCO) levels (median % COHb reduction: −1.6 and −1.28 for e-cigarettes and THS, respectively; $p < 0.001$ for both), reaching levels comparable to those of nonsmokers by the end of the study period [52]. Another investigation examined the effects of conventional combustible cigarettes and HTP aerosols on systemic inflammation in patients with ulcerative colitis (UC; $n = 74$), diabetes mellitus (DM; $n = 33$), and chronic obstructive pulmonary disease (COPD; $n = 78$). In patients with COPD, exposure to HTP aerosols was associated with enhanced production of immunosuppressive cytokines, including interleukin-10 (IL-10), IL-35, and the pro-fibrotic cytokine transforming growth factor-beta (TGF-β), while exerting a lesser effect on proinflammatory cytokines such as interferon-gamma (IFN-γ), IL-1β, IL-6, IL-22, IL-17, and tumor necrosis factor-alpha (TNF-α), compared with exposure to conventional cigarettes. In patients with DM, exposure to HTP aerosols was associated with increased concentrations of IL-10 and TGF-β and lower serum levels of proinflammatory cytokines, including TNF-α, IL-12, IFN-γ, IL-1β, IL-6, and IL-17, compared with exposure to conventional cigarettes. Both conventional cigarette smoke and HTP aerosols significantly modulated cytokine profiles in circulating immune cells, contributing to systemic inflammation in individuals with COPD and DM, but not in those with UC. These findings suggest that the immunomodulatory effects of both conventional cigarettes and HTP aerosols may be disease-specific, underscoring the need for further research to elucidate their roles in immune-mediated inflammatory diseases.

In a single-center, five-arm crossover study, the acute effects of two heated tobacco products (HTPs) and conventional cigarette consumption on small airway function were investigated in 17 healthy occasional smokers. Both small airway obstruction and resistance significantly increased after the consumption of conventional cigarettes and HTPs [40]. Similar results were observed in another crossover study involving 20 healthy subjects [42]. In a study conducted among cancer patients undergoing preoperative assessment, exclusive HTP users ($n = 92$) showed a lower prevalence of airway obstruction—defined as a ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) below the lower limit of normal—as compared to current conventional cigarette smokers ($n = 266$) (21.7% vs. 29.7%, respectively) [53]. In a prospective cohort study involving 1200 participants (400 HTP users and 800 conventional cigarette smokers) followed for 24 months, HTP use was associated with a smaller decline in lung function, as measured by FEV_1 (−0.0873, $p \leq 0.0001$) and six-minute walk distance (6MWD) (11.6988, $p \leq 0.0001$), as well as better COPD Assessment Test (CAT) scores (−1.7816, $p \leq 0.0001$) when compared with cigarette smoking [54]. In a three-year prospective study of 38 individuals with COPD, daily HTP users exhibited clinically significant improvements from baseline in CAT scores (−5, $p = 0.006$) and 6MWD (69 m, $p = 0.005$), along with a substantial reduction in the annual rate of COPD exacerbations (−0.8, $p = 0.004$) when compared with conventional cigarette smokers [55].

Discussion

This scoping review aimed to analyze the current evidence available in the scientific literature regarding the potential for HTPs to exhibit a different risk profile compared to conventional cigarettes, with a particular focus on cardiovascular and chronic respiratory diseases. HTPs have been commercially available for several years. Given their growing prevalence, there is considerable interest within the scientific and medical communities in determining whether these products present a modified risk profile compared to conventional cigarettes. Despite the heterogeneity of available data, current evidence suggests that HTPs exert a lower harmful impact on the cardiovascular and respiratory systems than conventional cigarettes. A recent article by Andreozzi et al. [5], which explored the effects of noncombustion alternatives to cigarette smoking—such as HTPs and electronic cigarettes—on chronic respiratory conditions, including COPD and asthma, concluded that although these products are not devoid of health risks, they are likely to be less harmful than conventional combustible cigarettes. Nonetheless, it is essential to highlight that the primary public health objective should remain complete smoking cessation and relapse prevention, in line with the principles of primary prevention. From a policy perspective, the present findings have implications for tobacco harm reduction strategies. Although promoting complete smoking quitting is the primary goal of cardiovascular and respiratory disease prevention, regulatory authorities could consider evidence-based differentiation between combustible conventional cigarettes and HTPs when designing risk communication policy. Human studies have shown that switching to HTPs is associated with significant reductions in blood and urinary biomarkers of tobacco-related toxicants, especially in cases of complete substitution. In the respiratory domain, some studies have reported that former smokers who transition to HTPs tend to experience lower odds of adverse respiratory outcomes, fewer exacerbations, and improvements in symptoms and physical performance compared to those who continue smoking or engage in dual use. Similar trends have also been observed in extensive population-based studies concerning cardiovascular risk [56].

These findings support the consideration of HTPs as potential tools for harm reduction, particularly among individuals who are unwilling or unable to quit smoking through conventional pharmacological or behavioral interventions, which often yield low long-term cessation rates. In alignment with broader public health principles, harm reduction represents a pragmatic medical strategy—especially when complete risk elimination is not feasible—and may be particularly relevant for individuals with chronic health conditions.

Nevertheless, considerable debate persists within the scientific community regarding the effectiveness of noncombustible alternatives, particularly e-cigarettes and HTPs, in promoting smoking cessation or reduction. Equally debated is the concern that such products may act as gateways to nicotine dependence and conventional smoking, particularly among tobacco-naïve individuals. While much of the available data pertains to e-cigarettes, there is growing concern over the increasing use of both e-cigarettes and HTPs among adolescents and young adults, with the potential for nicotine addiction, increased susceptibility to conventional cigarette use, and the resulting health threats [57, 58]. However, recent data from the United States indicate a decline in dual use among youth, suggesting a potentially less alarming trend [59].

A well-designed randomized controlled trial showed that switching to HTPs, in combination with motivational counseling, led to a significant reduction in cigarette consumption among smokers with no initial intention to quit. This suggests that HTPs may serve as valuable additions to the arsenal of reduced-risk alternatives to conventional cigarettes [60]. However, long-term follow-up studies are essential to assess sustained smoking abstinence and to determine whether these findings can be generalized beyond highly structured cessation programs that offer intensive support.

Given the relatively recent introduction of HTPs, in contrast to the long latency periods typically required for the development of smoking-related chronic diseases, as well as the evolving design and composition of these products, it is not surprising that definitive conclusions regarding their clinical and public health impact bring up the need to be integrated by long-term evidence derived from independently conducted studies. The lack of long-term studies represents a significant limitation in assessing the effect of HTP use on chronic disease outcomes. Most available studies focus on short-term biomarkers or physiological changes, which, although informative, cannot fully capture the cumulative effects of chronic exposure over decades. Long-term and large-scale prospective studies are therefore essential to establish the actual risk trajectory associated with sustained HTP use and its potential role in chronic disease prevention strategies.

Moreover, the interpretation of available evidence is complicated by marked heterogeneity across studies. The HTP devices evaluated differ considerably in design, heating temperature, tobacco substrate, and aerosol generation technology, all of which may influence emissions and toxicant profiles. Exposure protocols vary widely, including randomized and real-life studies, as well as acute and long-term observational follow-up, and product use durations. Outcome measures also differ from one biomarker level and physiological parameter to subjective symptom reports and clinical endpoints, making direct comparison difficult. In addition, study populations are heterogeneous, including healthy volunteers, current smokers, patients with pre-existing chronic diseases, and mixed samples, each with differing risk profiles. These variations highlight the need for standardized methodologies and harmonized reporting criteria to facilitate comparison between studies.

Several additional limitations of the studies included in this review, comparing the health effects of conventional cigarette smoking and HTP use, merit consideration. First, the potential for bias in study design, data analysis, and the selective reporting of favorable outcomes is a significant concern, particularly in industry-sponsored research. Furthermore, independent replication of findings remains limited. Nevertheless, some of the studies cited in this review focus on at-risk populations (i.e., smokers who do not quit despite having a smoking-related chronic disease), for whom evidence on the clinical effects of switching to combustion-free products appears to be relevant in any case. Second, the majority of available studies are of short duration, whereas tobacco-related diseases such as COPD and cardiovascular disease typically develop over extended periods, often spanning decades. Third, many studies rely on biomarkers or surrogate endpoints rather than hard clinical outcomes such as disease incidence, mortality, or hospitalization. Although surrogate measures are widely accepted in clinical research across various therapeutic areas and are valuable for early assessments, they may not fully reflect the long-term health effects of switching to HTPs. Nonetheless, the use of surrogate biomarkers can provide methodologically robust insights that, in some instances, serve to complement the available evidence on clinical outcomes.

In addition, many studies suffer from small sample sizes, with several ranging from 20 to 160 participants, and non-randomized designs, which limit their statistical power and generalizability. Finally, in real-world settings, dual use of HTPs and conventional cigarettes is highly prevalent and represents a critical issue that merits attention. Dual-use patterns may weaken the potential harm-reduction benefits of switching by maintaining exposure to combustion-related toxicants. Evidence suggests that partial substitution, rather than complete replacement, often produces limited health improvements. Given that dual use reflects real-world behavioral patterns, future studies should address this phenomenon from both behavioral and psychosocial perspectives to better understand its determinants and implications for public health outcomes.

These findings underscore the importance of conducting independent, high-quality research with adequate sample sizes and follow-up studies to accurately assess the long-term health implications of HTP use [61].

Conclusions

Preventing risk factors for chronic cardiovascular and respiratory diseases is one of the most critical challenges for healthcare systems. It involves adopting a healthy lifestyle, which certainly includes abstaining from tobacco smoking. The association of cigarette smoking with several severe and very severe diseases (oncological, cardiovascular, and respiratory), which have dramatic epidemiological, medical, social, and financial impacts, is a well-known public threat. In recent years, there has been a growing interest and use of alternative products to conventional cigarettes, in particular e-cigarettes and heated tobacco products, which are proposed and are perceived as modified risk products. This scoping review was focused on the comparison between conventional cigarettes and HTPs in the fields of cardiovascular and respiratory diseases. In our opinion, it provides a series of indications that can be summarized as follows:

- The currently available clinical studies confirm that the HTPs are not free from harmful effects, but in most cases, the risk appears reduced compared to conventional cigarettes.
- Every effort should be made to encourage and achieve smoking cessation, but a significant portion of smokers (sometimes patients as well) find quitting challenging or undesirable. In this specific setting, switching to HTPs could be a worthwhile consideration.
- There are many doubts about whether these products can help to reduce or stop smoking progressively. In addition to that, concerns about their role in promoting initiation among nonsmokers are a significant matter of debate.

- Strict epidemiological and medical monitoring is necessary in relation to the use of HTPs, as well as the acquisition of evidence from well-designed, independent studies with adequate sample sizes, follow-up, and clinically relevant endpoints.
- Globally, the growing need for clarity among citizens and healthcare providers regarding the characteristics of these products necessitates a specific commitment by institutions, scientific societies, and health associations to support activities of educational, informative, and preventive value, addressing a topic of significant health relevance.

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Declarations

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