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Review
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Review

Human Biomarker Exposure From Cigarettes Versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Novel tobacco products require independent research to assess their safety. This study assessed the current literature for trials comparing levels of biomarkers of exposure (BoE) between conventional cigarettes (CC) and heat-not-burn (HNB) devices.

Methods: Ten databases were searched using terms including: "heat not burn," "iqos," "teeps," "mrtp," "tobacco heating," and "glo" between January 1, 2010 and August 13, 2019. Randomized controlled trials (RCTs) assessing comparative BoE levels in humans using either CC or novel HNB devices were eligible. BoE were tabulated, and differences between the intervention and control groups were analyzed and combined using a random-effects meta-analysis.

Results: Ten nonblinded, RCTs were eligible, involving a total of 1766 participants. Studies regularly reported on 12 BoE (including nicotine). HNB devices assessed included the "IQOS" and "glo" devices and "precursor" (being developed) HNB devices. In comparison to CC, all 12 BoEs assessed were significantly lower for participants assigned to an HNB device. In comparison to smoking abstinence, HNB devices were statistically equivalent for eight BoEs and significantly elevated for four BoEs.

Conclusions: This review found that the potential for harm to humans is reduced when using HNB devices compared to CC as indicated by significant reductions in BoE levels. Whilst these results support tobacco manufacturer claims of improved safety, the small number of studies included, limited range of BoE assessed, and involvement of the tobacco industry necessitate further independent research to confirm the HNB devices as being a safer alternative to CC.

Implications: This study supports claims made by tobacco manufacturers on the improved safety of HNB tobacco devices in comparison to CC. These novel devices lead to reduced exposure to key biomarkers, which are linked to the health consequences attributed to tobacco use. This has strong implications for international public health as well as further research and policy development relating to the safety aspects and legalities of novel tobacco products.

Introduction

Tobacco use remains a leading preventable cause of morbidity and mortality and is linked to a growing array of health consequences, including lung cancer, chronic obstructive pulmonary disorder, and cardiovascular diseases.[1,2] An individual's risk of tobacco-attributable diseases is influenced by both their genetic predisposition and lifetime cumulative exposure to harmful tobacco product

constituents, including exposure to secondhand and thirdhand smoke.[3,4] Conventional cigarettes (CC) remain a primary method for the inhalation of tobacco smoke, which contains thousands of chemical constituents, many of which are known carcinogens. As global tobacco use is predicted to reach 1.5 billion smokers by 2050,[5] the World Health Organization and other public health stakeholders have attempted to manage the tobacco epidemic by recommending comprehensive tobacco control policies. This includes prohibiting advertising, regulating tobacco product appearance, and implementing tax increases.[6] However, tobacco manufacturers continue their attempts to circumvent these regulations to ensure the maintenance of the smoking culture and recruitment of the "next generation" of smokers.[7–10]

One such method for attracting and retaining smokers is the development and marketing of "heat-not-burn" (HNB) devices, which can resemble either electronic or CC in appearance and are promoted as "reduced-risk" tobacco products.[11] Unlike electronic cigarettes that utilize a nicotine-containing liquid or CC that achieve combustion by heating to at least 600ºC, these devices heat either a nicotine-free liquid, which passes through tobacco leaf, or heat-processed tobacco leaf to less than 350ºC. It is proposed that HNB devices are less harmful to human health than CC due to reduced exposure to carcinogens and other toxic constituents.[11,12] The earliest models of these HNB devices, such as "Premier," "Eclipse," and "Accord" were developed in the 1980s and 1990s. However, several issues were cited by smokers, including difficult operation and poor taste, which led to most of the early HNB devices being discontinued by the mid-2000s.[13,14] Following the poor uptake of these earlier models, emerging HNB devices include the "I Quit Original Smoking" (IQOS; Philip Morris International [PMI]) and "glo" (British American Tobacco [BAT]), which were first made available in Japan and Italy and have rapidly spread to other countries.[15]

If HNB devices are less harmful than CC, they could represent a method for harm reduction by allowing individuals to continue smoking behaviors and satisfying their nicotine addiction, whilst causing less harm to themselves and others. Assessing toxicant exposure and estimating health risks associated with tobacco products can be achieved through determining the levels of biomarkers of exposure (BoE). These are measures of exposure to "harmful and potentially harmful constituents" (HPHC) within tobacco products. The Institute of Medicine of the US Academy of Science defines a BoE as "a tobacco constituent or metabolite that is measured in a biological fluid or tissue that has the potential to interact with a biological macromolecule; sometimes considered a measure of internal dose."[16] BoE can, therefore, provide a more accurate assessment of health risk compared to the quantity of exposure (e.g., cigarettes per day) through utilizing a range of variables (tobacco and disease related), which allows the comparison of the relative harms of different tobacco products.[16]

The concept of a risk continuum by McNeill and Munafò places CC at the high-risk end, nicotine replacement therapy at the low-risk end and HNB products at a to-be-determined point in between.[17] Assessing the absolute risk of these devices is ongoing, with independent research required to guide relevant legislation and policy development. A recent (2018) independent review assessing the emissions, safety, and epidemiology of HNB products found that "switching from smoking cigarettes to using HNB significantly reduces but does not eliminate exposure to HPHC."[18] However, contradictory data released from PMI on their own IQOS device indicated there may be no significant difference in harm compared to CC.[19] Due to the debate on comparative safety between HNB products and CC and increasing public interest in these products,[20] we conducted a systematic review and meta-analysis to explore the safety profiles of HNB devices compared to CC. The underlying aim for this review was to evaluate comparative BoE levels resulting from the use of either CC versus novel HNB devices.

Methods

This systematic review is reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21]

Search Strategy and Study Eligibility

A systematic search strategy was used to identify original studies published in English between January 1, 2010 and August 13, 2019. The date limit was set to ensure the inclusion of articles relating to emerging HNB devices, such as "THS2.2" (IQOS) and "THP1.0" (glo), whilst excluding outdated precursor HNB devices, such as "Eclipse," "Accord," and "Premier." Ten databases were searched: CINAHL, Cochrane Library, EBSCO MegaFile Premier, EMBASE, Global Health, MEDLINE, ProQuest, PsycINFO, Scopus, and Web of Science. General search terms included "tobacco heating," "heat not burn," "HNB," "modified risk tobacco product," and "mrtp," and device-specific terms, such as "iqos," "teeps," and "glo." A full search strategy detailing the search terms, dates, and databases used is available in Supplementary Appendix 1. Citation and reference lists were scanned to identify additional eligible studies.

Studies eligible for inclusion were those that investigated the safety of HNB products in humans through assessing BoE levels compared to CC. Studies that investigated BoE or other safety data on mice, rats, or in vitro human tissue samples were ineligible as we intended to collect BoE data that results directly from human exposure. Studies that assessed the safety of electronic cigarettes or nonsafety-related aspects of HNB products, such as availability or public opinions, were also excluded, as were expert opinions and conference abstracts. Titles of potentially eligible studies were initially scanned by a single author (AD), with the assessment of the remaining studies for eligibility being performed by three authors (AD, SS, and TK). Abstracts were read by these authors, who independently cross-checked each other's lists of potentially eligible studies. Full texts were then read to assess for final eligibility, with disagreements resolved by consensus.

Data Extraction and Quality Appraisal

Two authors (AD and DB) were responsible for data extraction. Data items extracted were: author affiliations, source(s) of funding, year of publication, study type, country of participant recruitment, participant demographics (including smoking habits), intervention and control groups employed, participant numbers assigned to each group, duration of exposure to interventions, puffing topography, and biomarkers measured. The primary outcome of interest from these studies included differences in BoE levels after assignment to the intervention or control groups and comparative BoE differences between these groups.

Study quality was assessed by two authors (SS and TK) and checked by a third author (AD), with disagreements resolved by consensus. The Joanna Briggs Institute (JBI) critical appraisal checklist for randomized controlled trials (RCTs) was used to assess study

quality.[22] This validated 13-item checklist assesses study quality based on the method of randomization used, the similarity in participant characteristics between groups, level of blinding amongst the involved parties (including participants, those delivering treatment, and assessors), appropriateness of statistical analysis, and sources of selection and analytic bias. Due to the strong links between the eligible studies and tobacco manufacturers (including author employment and the provision of funding), the authors of this review were careful in assessing the sources and significance of bias in eligible articles. This included assessing the clarity of the descriptions provided relating to the equal treatment of participant groups, the method of randomization, outcome measurements, and appropriateness of trial design. Studies were considered as high quality if they sufficiently addressed 11 of the 13 JBI checklist items, moderate quality if they addressed between 7 and 10 of the criteria, and low quality if they addressed 6 or fewer of the criteria.

Data Synthesis and Analysis

Each BoE was assessed individually and compared between the HNB, CC, and abstinence (Abs) groups. Studies captured within this review all used a pre–post design with one or two control groups (CC and/or Abs). Standardized effect sizes (d) were, therefore, calculated according to the method recommended by Carlson and Schmidt,[23]

$$d = \frac{(T_{\text{post}} - T_{\text{pre}}) - (C_{\text{post}} - C_{\text{pre}})}{SD_{\text{pre}}}$$

where T_{post} and C_{post} are the postintervention means of the outcome in treatment and comparison groups, respectively, T_{pre} and C_{pre} are the corresponding preintervention means, and SD_{pre} is the pooled SD of the two groups at the preintervention time period. As d is a biased estimator with small sample sizes, we used the correction factor suggested by Hedges,[24] where n_i is the total sample size for the ith comparison (i.e., $n_i = n_T + n_C$):

$$J = 1 - \frac{3}{4 \times (n_i - 1) - 1}$$

The reported effect sizes (ES) are the product $d \times J$, with variance given by the equation below, where ρ is the correlation between the premeasurements and postmeasurements within a group:[25]

$$\text{Var}\,(\text{ES}) = 2J^2\,(1-\rho)\left(\frac{n_T + n_C}{n_T n_C}\right)\left(\frac{n_T + n_C - 2}{n_T + n_C - 4}\right)\left(1 + \frac{d^2}{2\,(1-\rho)\left(\frac{n_T + n_C}{n_T n_C}\right)}\right) - d^2$$

For trials where the means and SDs of the change (defined as post–pre) were available, this correlation was estimated for each group separately using:

$$\rho = \frac{\text{SD}_{\text{pre}}{}^2 + \text{SD}_{\text{post}}{}^2 - \text{SD}_{\text{diff}}{}^2}{2 \times \text{SD}_{\text{pre}} \times \text{SD}_{\text{post}}}$$

This was then averaged as appropriate for the ith comparison. However, in many instances, data on change was not available and we, therefore, imputed the average pre–post correlation from those trials which did report change. Sensitivity analyses were also conducted assuming $\rho = 0.1$ and $\rho = 0.9$ for all studies. After a standardized effect size and corresponding confidence interval was calculated for each study using the above, the overall effect size estimate was combined using a random-effects model according to the method of DerSimonian and Laird.[26]

Results

Search Results and Study Characteristics

The search strategy yielded 4123 results, which after de-duplication from the multiple databases resulted in 1397 unique studies. Initial title screening by AD excluded 813 studies, with the remaining 584 studies assessed for eligibility by three authors (AD, SS, and TK). Abstract screening excluded a further 549 studies, leaving 35 for full-text review. Full-text review excluded a further 25, leaving 10 eligible studies included in this systematic review and meta-analysis. Figure 1 details the results of the systematic search.

Across the 10 studies, 21 BoE (including nicotine) were reported. Biomarkers were collected throughout the intervention period via 24-h urine samples and daily blood samples in the six studies that had a confinement period and at set points in those with an ambulatory period. To limit the number of biomarkers being assessed and to ensure meaningful outcomes through a sufficient quantity of data, only biomarkers that were reported in at least 8 of the 10 eligible studies were analyzed. Twelve biomarkers met this criteria: 1-hydroxypyrene (1-OHP), 2-aminoaphthalene (2-AN), 3-cyanoethylmercapturic acid (CEMA), 3-hydroxypropylmercaptauric acid (3-HPMA), 4-aminobiphenyl (4-ABP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), carboxyhemoglobin (COHb), monohydroxybutenyl-mercapturic acid (MHBMA), n-nitrosonornicotine (NNN), o-toluidine (0-tol), s-phenylmercapturic acid (S-PMA), and total nicotine equivalents (TNeq). Supplementary Appendix 2 lists the 21 BoEs evaluated throughout the studies, their attributed HPHCs, and the 12 BoE that were eligible and assessed in this review (bolded).

A total of 1766 participants were involved in the 10 studies that were conducted in Japan, Poland, or the United States. Table 1 details the study characteristics and participant demographics. Most studies utilized an RCT design, except for one semi-RCT design.[27] Common participant exclusion criteria were: inadequate contraception, pregnant or breastfeeding, recent blood donation, current acute illness, recent non-cigarette tobacco use, planned to quit smoking within 12 months, or had abnormal laboratory tests (physical, medical, ECG, lung function, or laboratory panel). All studies had most or all of the authors employed by a tobacco manufacturer, and all studies were funded by these manufacturers. After baseline measurements, participants were allocated to continue smoking CC, exclusively use an HNB device, or be completely abstinent from nicotine products.

CC used were the smokers' usual brand, except for two studies that provided cigarettes.[27,32] HNB devices included the commercially available "glo" and "IQOS," as well as "precursor" products, which include devices still under development and earlier device models that have been refined and are now commercially available. Nicotine quantity in the HNB devices ranged from 0.3 to 1.21 mg per stick or capsule. These devices all include a rechargeable battery-powered heating element and an insertable capsule or stick that contains processed tobacco leaf. Some also contain a nicotine-free liquid, which is heated (instead of the tobacco leaf) into a vapor that passes through the tobacco, drawing out the nicotine and flavors. After baseline measurements and allocation, the intervention period ran for 5 days

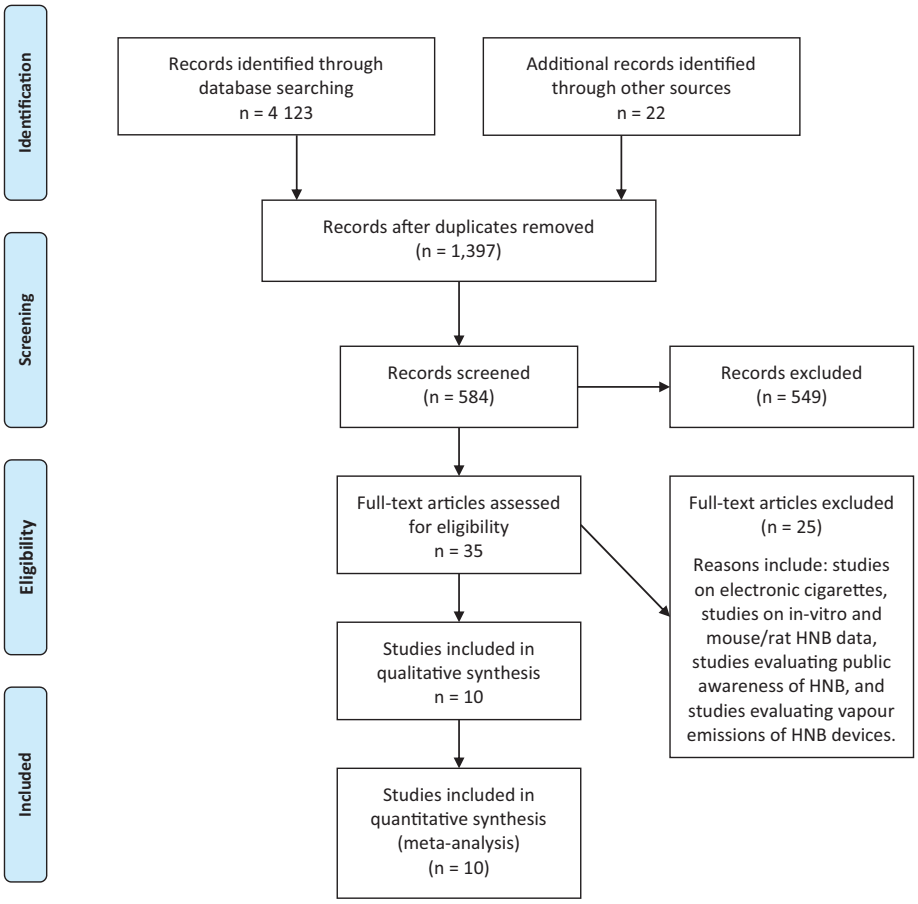

Figure 1. Flowchart of the systematic search strategy.

in confinement in six studies,[28–32,34] 28 days in a residential setting in one study,[27] 5 days in confinement followed by 85 days ambulatory in two studies study,[33,35] and a 6-month ambulatory period in one study.[36] For consistency across the studies, those that collected data both during confinement and in an ambulatory setting only had their confinement data analyzed. Confinement involved physical restriction to the clinic for the duration of the intervention period and supervised smoking only in smoking rooms during approved hours (6:30 AM to 11:00 PM in most studies). HNB sticks or capsules and CC were provided one at a time upon participant request, with puffing topography (number of puffs, total puff volume, and puff duration) recorded throughout the confinement period in most of the studies.[27–31,33,34]

Quality Appraisal

The JBI quality appraisal checklist found all 10 studies as being of moderate quality, scoring 8 or 9 out of 13. Four of the checklist items were commonly unmet by these studies due to study design and being unable to blind participants or researchers (checklist items 2, 4, 5, and 6). This lack of blinding was due to the obvious and unavoidable differences in the interventions used between the different arms of these studies (CC, HNB, or abstinence). A lack of clarity on the method of randomization used (checklist item 1) was a further issue with some of the studies. An additional consideration relating to reporting bias is that all 10 studies had one or more of the authors employed by PMI, BAT, or Japan Tobacco Inc, with these companies also funding the research. Due to the small number of studies available and the unavoidable issues arising from trial design (relating to blinding), their inclusion in the analysis was necessary.

Product use and BoE

Biomarker data were extracted from the full analysis set for most studies, except for two that used the per protocol set.[33,35] Total daily use of HNB and CC use was unrestricted in all but two studies, one which restricted both HNB and CC use to 125% of usual daily cigarette consumption[32] and one which restricted CC use to within 10% of usual cigarette consumption and HNB to 10 capsules per day.[34] In six unrestricted-use studies, the total number of HNB capsules or sticks used were generally comparable to the number of CC. However, total puff volume, number of puffs, and puff duration were increased for HNB devices compared to CC in four of these studies,[27,28,30,31] and comparable in the remaining two studies.[29,33] In the four studies with different puffing behaviors, total puff volume increased by 5%–27%, number of puffs by 19%–40%, and puff duration by approximately 33%.[27,28,30,31] In the study which strictly limited consumption of CC (within 10% of normal use), total puff volume increased by nearly 200%, 30% increased puff duration, and 50% increased puff number for HNB participants.[34]

Table 1. Characteristics of the studies eligible for inclusion in this meta-analysis (n = 10)

Study	Location (funder[1]) and JBI score[2]	Intervention period and setting	Total[3] participants	No. of male: female[3]	Age range (years)	Smoking habits	Conventional cigarette participant[2]	Intervention participant[2]	Abstinent participant[2]
Sakaguchi et al.[27]	Japan (JTI) 8	28 d (ambulatory)	69	69:0	21–49	≥20 CPD for >12 mo	23	46 (precursor)	—
Haziza et al.[28]	Japan (PMI) 8	5 d (confinement)	158	80:80	23–65	≥10 CPD for >3 y	40	80 (IQOS)	38
Haziza[4] et al.[29]	Poland (PMI) 9	5 d (confinement)	159	80:79	21–65	≥10 CPD for >3 y	41	79 (IQOS)	39
Lüdicke et al.[30]	Poland (PMI) 9	5 d (confinement)	112	56:56	23–55	≥10 CPD for >5 y	28	56 (precursor)	28
Lüdicke et al.[31]	Poland (PMI) 9	5 d (confinement)	40	19:23	23–65	≥10 CPD for >3 y	20	20 (precursor)	—
Gale et al.[32]	Japan (BAT) 9	5 d (confinement)	180	90:90	23–55	≥10 CPD for >3 y	60	60 (glo) 30 (IQOS)	30
Lüdicke et al.[33]	Japan (PMI) 9	5 d (confinement) 85 d (ambulatory)	155	92:68	23–65	≥10 CPD for >3 y	41	76 (precursor)	38
Yuki et al.[34]	Japan (JTI) 9	5 d (confinement)	60	42:18	21–65	≥11 CPD for >12 mo	20	20 (precursor)	20
Haziza et al.[35]	United States (PMI) 9	5 d (confinement) 85 d (ambulatory)	160	96:64	22–66	≥10 CPD for >3 y	41	80 (IQOS)	39
Lüdicke et al.[36]	United States (PMI) 9	6 mo (ambulatory)	673	397:276	30–65	≥10 CPD for >10 y	428	245 (IQOS)	—

CPD: cigarettes per day.

[1]JTI: Japan Tobacco Inc; PMI: Philip Morris International; BAT: British American Tobacco.

[2]JBI: Joanna Briggs Institute quality checklist, which had a maximum score of 13.

[3]Total number of participants completing the study and the number of participants assigned to the intervention groups before dropout.

[4]Haziza et al. published a second article including data relating to this study.[37]

Table 2. Biomarkers of Exposure (BoE) effect sizes (SDs) and p-values for the heat-not-burn (HNB) group versus conventional cigarette (CC) and abstinence (Abs) groups

BoE	Comparison	Effect size (SD) and 95% confidence interval	p-value
2-aminoaphthalene	HNB vs. CC	−1.77 (−2.07, −1.46)	<.001
(2-AN)	HNB vs. Abs	−0.08 (−0.26, 0.09)	.367
Carboxyhemoglobin	HNB vs. CC	−1.72 (−2.48, −0.97)	<.001
(CoHB)	HNB vs. Abs	0.14 (−0.08, 0.37)	.213
4-aminobiphenyl	HNB vs. CC	−1.53 (−1.76, −1.30)	<.001
(4-ABP)	HNB vs. Abs	−0.04 (−0.22, 0.13)	.639
2-cyanoethylmercapturic acid	HNB vs. CC	−1.38 (−1.79, −0.98)	<.001
(CEMA)	HNB vs. Abs	−0.04 (−0.19, 0.11)	.640
3-hydroxypropylmercaptapuric acid	HNB vs. CC	−1.22 (−1.63, −0.82)	<.001
(3-HPMA)	HNB vs. Abs	0.21 (0.02, 0.40)	.027
1-hydroxypyrene	HNB vs. CC	−1.17 (−1.53, −0.80)	<.001
(1-OHP)	HNB vs. Abs	−0.08 (−0.21, 0.05)	.233
s-phenylmercapturic acid	HNB vs. CC	−1.14 (−1.35, −0.94)	<.001
(S-PMA)	HNB vs. Abs	−0.10 (−0.28, 0.08)	.275
o-toluidine	HNB vs. CC	−1.03 (−1.25, −0.80)	<.001
(o-tol)	HNB vs. Abs	−0.00 (−0.16, 0.16)	.988
Monohydroxybutenyl-mercapturic acid (MHBMA)	HNB vs. CC	−0.93 (−1.21, −0.66)	<.001
	HNB vs. Abs	−0.14 (−0.35, 0.07)	.192
n-nitrosonornicotine	HNB vs. CC	−0.82 (−1.15, −0.48)	<.001
(NNN)	HNB vs. Abs	0.22 (0.01, 0.43)	.041
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)	HNB vs. CC	−0.65 (−0.82, −0.48)	<.001
	HNB vs. Abs	0.11 (0.03, 0.18)	.005
Total nicotine equivalents	HNB vs. CC	−0.37 (−0.70, −0.05)	.023
(TNeq)	HNB vs. Abs	1.91 (1.40, 2.41)	<.001

Despite the increases in HNB use in these studies, the levels of all 12 BoEs analyzed in this meta-analysis were significantly lower in the HNB participants compared to those assigned to CC. Table 2 outlines the effect sizes of the 12 BoE for the comparisons between the intervention and control groups in descending order of effect size for HNB versus CC. Figure 2 illustrates (via forest plot) these effect

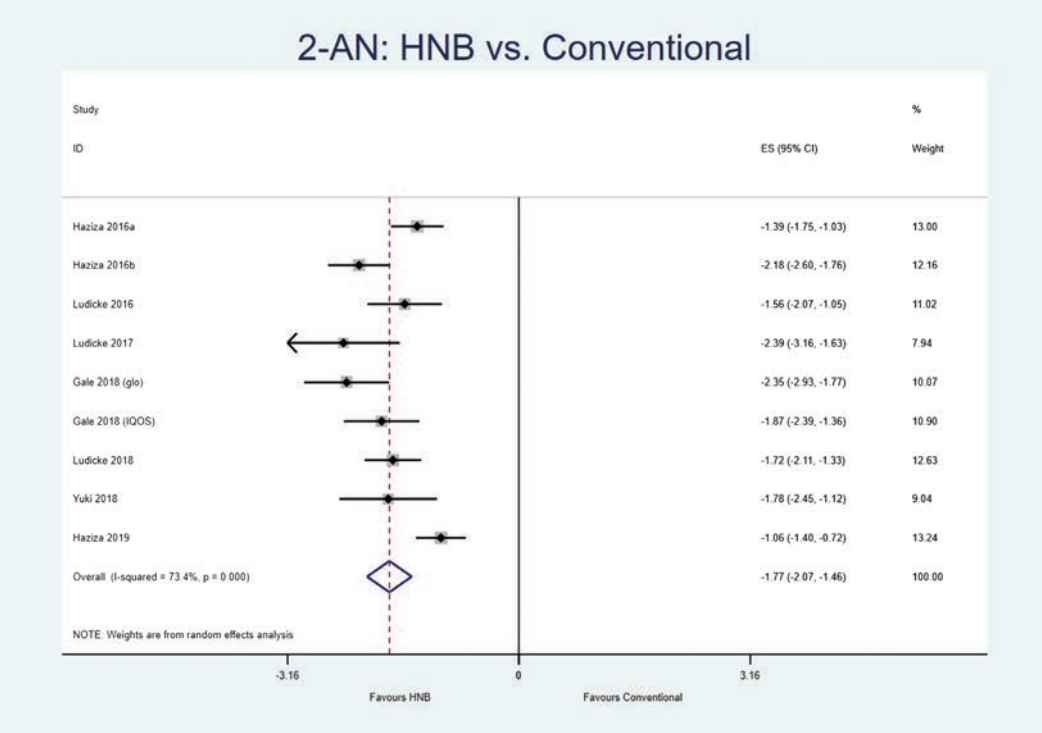

Figure 2. The forest plot illustrating the postexposure mean differences in 2-aminoaphthalene (2-AN) between heat-not-burn (HNB) and conventional cigarettes (CC).

sizes for each BoE, with the full set of 24 forest plots available in Supplementary Appendix 3. The most significant reductions between these two intervention groups were seen for 2-AN, COHb, 4-ABP, and CEMA, all with negative effect sizes (SDs) of 1.2 or greater. TNeq exposure was the BoE least different between the two groups. In comparison to the abstinence group, the levels of 8 of 12 BoEs for HNB participants were not statistically different, whereas the BoEs 3-HPMA, NNN, NNAL, and TNeq were significantly higher in the HNB participants. TNeq had the greatest difference between the two groups, with a positive effect size of 1.91, whereas 3-HPMA, NNN, and NNAL had positive effect sizes of less than 0.25.

Discussion

Potential modified risk tobacco products, such as the "IQOS" and "glo" HNB devices, have been developed by tobacco manufacturers in response to the growing dissent for CC. Manufacturers claim these devices provide an alternative source of nicotine with significantly reduced risk to users. This study aimed to evaluate these claims relating to the relative safety of HNB products compared to CC. The analyses conducted in this study support these claims, with the levels of all 12 BoEs evaluated being significantly lower in the HNB participants compared to the CC participants. These reductions were apparent even with changes in puffing topography, including increased puff volume, puff duration, and number of puffs in those assigned to HNB devices compared to CC. In addition, levels of 8 of the 12 BoEs in HNB participants were not significantly different to smoking abstinence, indicating that, although they may have improved safety over CC, the complete safety of HNB devices cannot be assured.

As described by Murphy et al., arbitrary placement on the risk continuum can be rectified by supporting science that allows accurate placement and comparison of the relative safety of the various tobacco products available.[38] It is, therefore, necessary to distinguish different potential modified risk tobacco products along this continuum, such as e-cigarettes and HNB devices, as well as the differences between individual HNB devices.[17,38] A recent review by Simonavicius et al. assessed HNB emissions, as well as BoEs from many of the RCTs analyzed in the current study stated, "evidence on HNB second-hand emissions suggested that HNB exposes users and bystanders to substantially lower but measurable levels of particulate matter and HPHC".[18] The authors also described differences in potential harm between individual HNB devices, with the aerosol of IQOS containing the highest proportional levels of nicotine and HPHCs, followed by glo, and then the iFuse device.[18] These findings indicate that safety cannot be assured for HNB devices, neither for the smoker nor close contacts, and that individual HNB devices may also have different relative levels of safety. Similar to the findings of the current study, Simonavicius et al. also noted that HNB participants utilized compensatory puffing techniques, which may have resulted from lower nicotine exposure per puff with HNB devices.[18] Furthermore, the potential public health benefits of HNB devices may be marred by dual use of these devices with CC, which has been the case to some extent for electronic cigarettes.[39] Dual use would substantially reduce the health benefits of HNB devices by inhibiting the reduction in biomarkers of exposure. A concern related to this finding is the issue of addiction development itself and the potential for the normalization of smoking behaviors using devices that are marketed as "reduced risk."[40]

Health risk estimation can be achieved through the linking of individual BoEs to specific health consequences resulting from exposure to inform on the relative risk of different tobacco products. Both COHb and 2-AN had the greatest reductions in exposure between HNB devices and CC. COHb levels are elevated several times above normal in tobacco smokers,[41] with the resulting displacement of oxygen from hemoglobin not only leading to headaches, dizziness, and gastrointestinal upset but also increasing the risk of atherosclerosis.[42,43] Similarly, 2-AN and 4-ABP are known carcinogens suspected to contribute to bladder cancer.[44,45] Replacement of CC with an HNB device may, therefore, confer some level of protection against these health consequences that are often attributed to smoking. However, NNN and NNAL were elevated in comparison to abstinence and are linked to respiratory and pancreatic cancers, signifying continued safety concerns.[45,46] Quantifying measurable outcomes, such as BoEs, contribute to the goal of assessing relative safety and allow substantiation of claims for the reduced potential for harm of HNB devices. To date, two small independent studies have evaluated comparative levels of a single BoE (carbon monoxide) between IQOS, glo, and e-cigarettes and reported finding no or minimal differences.[47,48]

Based on the findings of the current study, further research is required to understand to what degree these "potential modified risk tobacco products" differ in their delivery of nicotine and HPHCs and the resulting levels of key BoEs in smokers and close-contact nonsmokers. This includes the potential for secondhand smoke from HNB devices to raise BoE levels in nonsmokers. Transparent and standardized independent research utilizing clear protocols is required to allow the comparison and interpretation of multiple, large datasets relating to the safety of these emerging tobacco products. Similar recommendations were made recently by Hendlin et al. in a systematic review of financial conflicts of interest and harm reduction.[49] Postmarketing surveillance of the spread and uptake of HNB devices is also needed to identify key population groups exposed to these devices, such as adolescents, who may have altered pharmacokinetic profiles for HPHCs compared to the adult participants in this review. Adverse event data was also minimal in these studies due to the short duration of exposure, and long-term safety data would need to include comparative adverse event profiles between HNB and conventional tobacco products.

Limitations

There are limitations within this review as well as the eligible studies to consider when interpreting and applying these findings. Most notable is the involvement of the tobacco industry in the each of the studies included in this review, with author affiliations and funding issues introducing concerns relating to reporting bias.[50–52] An additional consideration is that most studies had a short duration of exposure to the intervention materials. Confinement studies such as these are more informative and reliable than ambulatory studies through having more control over participant exposure, although they prevent an assessment of the long-term effects of HNB devices on BoEs. Confinement may have also affected participants' urge to smoke through a reduction in their normal environmental cues, affecting the generalizability of these results to real-world conditions, and an overstatement of the potential health benefits of HNB devices. In addition, there was a limited range of BoEs analyzed due to inconsistency in the reporting of BoEs within the individual studies, preventing a more complete estimation of comparative levels of harm between HNBs and CC. Most of the studies were conducted in either Poland or Japan, which may confound the results due to metabolic differences between these populations and those from other countries and ethnicities. Precursor products in this review were in some cases not marketed and, with further development, led to reductions in toxicant exposure and an underestimation of their total comparative safety to CC. Finally, the moderate quality of the studies identified through the quality appraisal tool (largely related to the unavoidable lack of blinding) requires that the results be interpreted and applied with caution.

Conclusions

HNB devices, such as "IQOS" and "glo" are marketed as "reduced-risk" tobacco products and are claimed to reduce harm to smokers compared to CC. This review supports these claims, with all 12 BoEs that were analyzed being significantly lower in the HNB participants compared to those using CC. These BoE reductions were greatest for several known carcinogens, including COHb, 2-AN, 4-ABP, and CEMA, indicating the potential for significantly reduced harm when using HNB devices in comparison to CC. In addition, levels of 8 of the 12 BoEs were statistically equivalent between the HNB and abstinence participants, though the levels of some carcinogenic BoEs were significantly increased. HNB devices, therefore, may have a role in harm reduction, although it should not be considered as wholly safe. The strong involvement of tobacco manufacturers in these studies demonstrates the need for caution in interpreting these findings and the need for independent research to be conducted to either confirm or refute these findings.

Supplementary Material

Supplementary data are available at *Nicotine and Tobacco Research* online.

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Declaration of Interest

The authors declare no competing interests.

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