The impact of heated tobacco products on biomarkers of potential harm and adverse events: a systematic review and meta-analysis

Supplementary Materials

Contents

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Supplementary Appendix 1. Coding of trial affiliation.

Trials were coded as 'Industry-affiliated' if:

- the study sponsor named on the trial registration was a tobacco company or other organisation directly funded by a tobacco company; or
- funding statements in any of the trial literature indicated the trial was funded in part or in whole by a tobacco company or other organisation directly funded by a tobacco company; or
- author affiliations or conflict of interest statements indicated any author was an employee or funded by a tobacco company or other organisation directly funded by a tobacco company at the time of the trial.

Trials were coded as 'Independent' if:

- the sponsor named on the trial registration had no known ties to the tobacco industry; and
- funding statements in any of the trial literature indicated the trial was not funded by a tobacco company or other organisation funded by a tobacco company; and
- author affiliations and conflict of interest statements indicated authors had no contemporary (i.e., while the study was being conducted, up to and including publication) ties to the tobacco industry.

Trials were coded as 'Unclear' if:

- There was insufficient information to determine affiliation; or
- Reviewers could not reach consensus.

In addition to conflict of interest and funding statements provided in the trial literature, we further investigated known ties and funding using the Tobacco Tactics website (www.tobaccotactics.org), relevant literature published by the Tobacco Control Research Group (University of Bath), and conflict of interest and funding statements in other contemporary work of the authors of included studies.

Supplementary Table 1. Direction of effect indicative of harm for each biomarker, alongside supporting literature in addition to the reporting in the original study.

	Biomarker	Direction indicating harm	Additional supporting literature
Cardiovascular function	A wave velocity	↑	https://doi.org/10.1111/echo.14514; https://doi.org/10.1016/j.jsha.2013.03.003
	Arterial Blood Pressure	↑	https://doi.org/10.1093/ntr/ntx273
	Augmentation index	↑	https://doi.org/10.1093/eurheartj/ehq024; https://doi.org/10.1161/CIRCULATIONAHA.104.482570
	Central pulse pressure	↑	https://doi.org/10.1093/ntr/ntx273; https://www.ncbi.nlm.nih.gov/books/NBK482408/; https://doi.org/10.1093/eurheartj/ehq024
	Diastolic blood pressure	↑	https://doi.org/10.1093/ntr/ntx273
	E wave velocity	↓	https://doi.org/10.1111/echo.14514; https://doi.org/10.1016/j.jsha.2013.03.003
	E wave/A wave ratio	↓	https://brieflands.com/articles/ircrj-132828.pdf; https://doi.org/10.1111/echo.14514; https://doi.org/10.1016/j.jsha.2013.03.003
	Heart rate	↑	https://doi.org/10.1093/ntr/ntx273
	Left atrium diameter	↑	https://doi.org/10.1111/echo.14514
	Left ventricle early/late diastolic mitral annulus tissue Doppler velocities ratio	↓	https://doi.org/10.1111/echo.14514
	Left ventricle ejection fraction	↓	https://brieflands.com/articles/ircrj-132828.pdf
	Left ventricle global circumferential strain	↓	https://brieflands.com/articles/ircrj-132828.pdf
	Left ventricle global longitudinal strain	↓	https://doi.org/10.1111/echo.14514
	Left ventricle peak early diastolic velocity	↓	https://brieflands.com/articles/ircrj-132828.pdf; https://doi.org/10.1111/echo.14514
	Left ventricle peak late diastolic velocity	↑	https://doi.org/10.1111/echo.14514
	Left ventricle systolic myocardial velocity	↑	https://doi.org/10.1111/echo.14514
	Left ventricular end-diastolic diameter	↑	https://doi.org/10.1111/echo.14514
	Pulse wave velocity	↑	https://doi.org/10.1016/j.jacc.2007.10.065; https://doi.org/10.1161/CIRCULATIONAHA.105.555235; https://doi.org/10.1161/CIRCULATIONAHA.104.482570
	Right atrium diameter	↑	https://doi.org/10.1111/echo.14514
	Right ventricle diameter	↑	https://doi.org/10.1111/echo.14514
	Right ventricle early/late diastolic mitral annulus tissue Doppler velocities ratio	↓	https://doi.org/10.1111/echo.14514
	Right ventricle free wall strain	↓	https://doi.org/10.1111/echo.14514
	Right ventricle global longitudinal strain	↓	https://doi.org/10.1111/echo.14514
	Right ventricle peak early diastolic velocity	↓	https://doi.org/10.1111/echo.14514
	Right ventricle peak late	↑	https://doi.org/10.1111/echo.14514

	diastolic velocity		
	Right ventricle systolic myocardial velocity	↑	https://doi.org/10.1111/echo.14514
	Systolic blood pressure	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1093/eurheartj/ehq024
	Total extracellular vesicles	↑	https://doi.org/10.3389/fcvm.2022.907457; https://doi.org/10.1161/CIRCRESAHA.117.310752
	Total Peripheral Resistance	↑	https://doi.org/10.1161/01.HYP.28.1.37; https://www.ncbi.nlm.nih.gov/books/NBK538308/
	Tricuspid annular plane systolic excursion	↓	https://brieflands.com/articles/ircrj-132828.pdf; https://doi.org/10.1016/j.jsha.2013.03.003
Endothelial dysfunction	Albumin (in urine)	↑	https://doi.org/10.1161/CIRCULATIONAHA.104.482570; https://doi.org/10.1080/1354750X.2017.1419284
	Endothelial-derived extracellular vesicles	↑	https://doi.org/10.1093/ntr/ntx273
	Flow-mediated dilation	↓	https://doi.org/10.1093/ntr/ntx273
	Nitric oxide bioavailability	↓	https://doi.org/10.1161/01.CIR.0000153339.27064.14; https://doi.org/10.1016/j.ccc.2019.12.009; https://doi.org/10.3390/molecules27227921
	Soluble intercellular adhesion molecule-1	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
Inflammation	Chemokine (C-C motif) ligand 7	↑	https://doi.org/10.1172/jci.insight.132048; https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1016/j.cyto.2023.156403
	Chemokine (C-X-C motif) ligand 1	↑	https://doi.org/10.1002/jlb.59.1.67; https://doi.org/10.1152/ajplung.00074.2015
	Chemokine (C-X-C motif) ligand 10	↓	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1158/1078-0432.ccr-19-1769; https://doi.org/10.1016/j.rmed.2019.105822; https://urn.fi/URN:NBN:fi-fe2023042438477
	C-reactive protein	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	Eotaxin-1	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1080/02770900902846349; https://doi.org/10.4049/jimmunol.178.8.5321
	Epidermal growth factor (saliva)	↓	https://doi.org/10.1152/ajpgi.2000.278.1.g10; https://doi.org/10.1016/0300-483x(92)90153-6
	Fms-related tyrosine kinase 3 ligand	↑	https://doi.org/10.3389/fimmu.2024.1416870; https://doi.org/10.1183/13993003.00277-2024
	Granulocyte-macrophage colony-stimulating factor	↑	https://doi.org/10.1016/j.jaut.2009.12.003; https://doi.org/10.1152/ajplung.00074.2015
	High-sensitivity C-reactive protein	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	Homocysteine	↑	https://doi.org/10.1001/jama.288.16.2015; https://doi.org/10.1080/1354750X.2017.1419284
	Interferon alpha-2	↑	https://doi.org/10.3390/biomedicines12040748
	Interferon-gamma	↓	https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.21037/tlcr.2019.03.02
	Interleukin-1 alpha	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.5021/ad.2014.26.1.11
	Interleukin-1 beta	↑	https://doi.org/10.3390/molecules27123715; https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015
	Interleukin-1 receptor antagonist	↑	https://www.europeanreview.org/article/7005; https://doi.org/10.2337/dc08-1161
	Interleukin-10	↓	https://doi.org/10.7150/ijms.13800; https://doi.org/10.1155/2014/158530; https://doi.org/10.1152/ajplung.00074.2015;

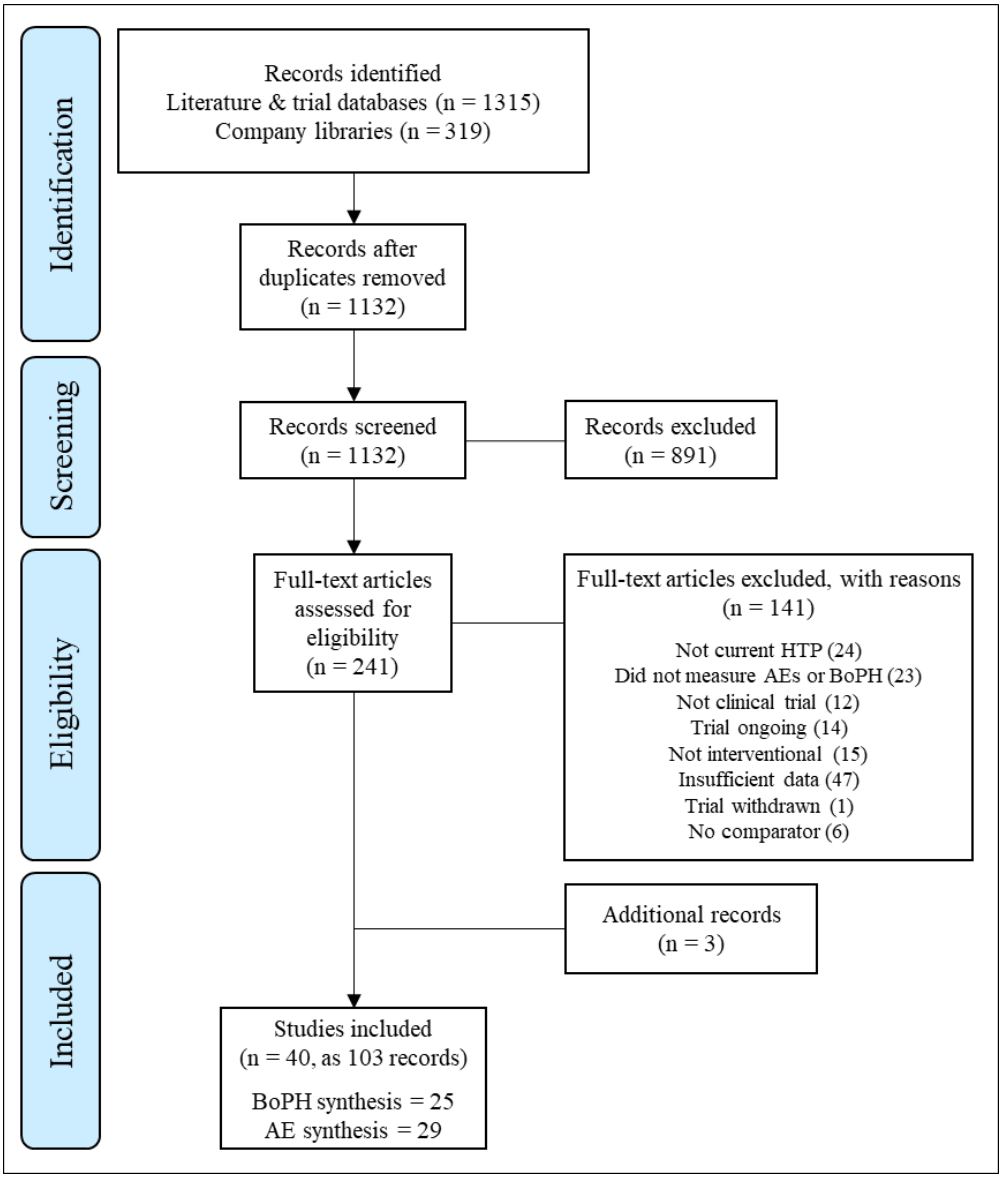
			https://doi.org/10.1016/j.jaut.2009.12.003
	Interleukin-12	↑	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1155/2014/158530
	Interleukin-12 beta	↓	https://doi.org/10.4049/jimmunol.181.2.1536; https://doi.org/10.1038/s41598-021-91510-x
	Interleukin-13	↑	https://doi.org/10.3390/diseases12070144; http://dx.doi.org/10.1165/rcmb.2009-0117OC
	Interleukin-15	↑	https://doi.org/10.1186/s12903-022-02700-6
	Interleukin-17	↑	https://doi.org/10.3390/diseases12070144
	Interleukin-2	↓	https://doi.org/10.1067/mai.2000.107751; https://doi.org/10.1152/ajplung.00074.2015
	Interleukin-3	↑	https://doi.org/10.1084/jem.20180722; https://doi.org/10.3389/fimmu.2024.1411047
	Interleukin-4	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1111/j.1365-2249.1994.tb06533.x
	Interleukin-5	↑	https://pubmed.ncbi.nlm.nih.gov/24706315/
	Interleukin-6	↑	https://doi.org/10.1016/j.jaut.2009.12.003; https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1152/ajplung.00074.2015
	Interleukin-7	↓	https://doi.org/10.1152/ajplung.00074.2015; http://dx.doi.org/10.1186/1471-2431-13-57; https://doi.org/10.1016/j.sjbs.2019.11.001
	Interleukin-8	↑	https://doi.org/10.1016/j.jaut.2009.12.003; https://doi.org/10.1038/s41598-020-68753-1
	Interleukin-9	↓	https://doi.org/10.3390/biomedicines12040748; https://doi.org/10.1183/23120541.00639-2021
	Leukocyte-derived extracellular vesicles	↑	https://doi.org/10.1155/2018/4692081; https://doi.org/10.3390/ijms25010388
	Lymphotoxin-alpha	↑	https://doi.org/10.1152/ajplung.00074.2015
	Macrophage inflammatory protein-1 alpha	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.3109/01902149409031733; https://doi.org/10.1007/s00262-006-0149-3
	Macrophage inflammatory protein-1 beta	↑	https://doi.org/10.1007/s00262-006-0149-3; https://doi.org/10.1152/ajplung.00074.2015
	Macrophage-derived chemokine	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1016/j.clim.2005.03.001; https://doi.org/10.1038/s41598-020-68753-1
	Matrix metalloproteinase-1	↑	https://doi.org/10.1161/01.ATV.0000199268.27395.4f; https://doi.org/10.7150/ijms.79889
	Matrix metalloproteinase-10	↑	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
	Matrix metalloproteinase-12	↑	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
	Matrix metalloproteinase-13	↑	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
	Matrix metalloproteinase-8	↑	https://doi.org/10.1161/01.ATV.0000199268.27395.4f
	Matrix metalloproteinase-9	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.4274/MMJ.galenos.2022.45057
	Monocyte chemotactic protein-1	↑	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.4274/MMJ.galenos.2022.45057
	Neutrophil-derived extracellular vesicles	↑	https://doi.org/10.1155/2018/4692081; https://doi.org/10.3390/ijms25010388
	Osteoprotegerin	↓	https://doi.org/10.1016/j.archoralbio.2020.104714; https://doi.org/10.1111/j.1600-051x.2007.01048.x; https://doi.org/10.4103/2277-9175.180992;

			https://doi.org/10.3390/jcm8030406
	Platelet derived growth factor isoform AA	↓	https://doi.org/10.1164/rccm.200605-585OC; https://doi.org/10.1007/s10006-025-01345-3; https://doi.org/10.3892/etm.2019.8025
	Platelet derived growth factor isoform AB/BB	↓	https://doi.org/10.1164/rccm.200605-585OC; https://doi.org/10.1007/s10006-025-01345-3; https://doi.org/10.3892/etm.2019.8025
	Receptor activator nuclear kappa B ligand	↑	https://doi.org/10.1155/2014/731039
	Regulated upon activation normal T-cell expressed and secreted	↑	https://doi.org/10.1152/ajplung.00074.2015; https://doi.org/10.1093/toxsci/kfj147; https://doi.org/10.4049/jimmunol.166.1.552
	Tissue inhibitor of metalloproteinase-1	↑	https://doi.org/10.4274/MMJ.galenos.2022.45057
	Transforming growth factor alpha	↑	https://doi.org/10.1002/jat.4469
	Tumor necrosis factor alpha	↑	https://doi.org/10.1016/j.jaut.2009.12.003; https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.3390/diseases12070144
	White blood cell count	↑	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1080/1354750X.2017.1419284
Respiratory function	Carbon monoxide transfer coefficient	↓	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3229853/; https://www.ncbi.nlm.nih.gov/books/NBK556149/
	Central obstruction	↑	https://doi.org/10.1016/j.rmed.2003.09.005; https://doi.org/10.4103/0970-2113.184875; https://doi.org/10.1016/S0140-6736(22)00470-6
	Diffusion Capacity for CO	↓	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/; https://www.ncbi.nlm.nih.gov/books/NBK556149/
	Forced expiratory flow at 25–75% of forced vital capacity	↓	https://pubmed.ncbi.nlm.nih.gov/12841492/
	Forced expiratory volume	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	Forced expiratory volume in the first one second/forced vital capacity	↓	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/; https://pubmed.ncbi.nlm.nih.gov/12841492/
	Forced vital capacity	↓	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/; https://pubmed.ncbi.nlm.nih.gov/12841492/
	Fractional exhaled nitric oxide	↓	https://doi.org/10.1136/thorax.58.2.175; https://doi.org/10.1080/00039890009604040; https://doi.org/10.5402/2011/832560; https://doi.org/10.1183/09031936.06.00113705
	Functional residual capacity	↓	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/
	Inspiratory capacity	↓	https://pubmed.ncbi.nlm.nih.gov/12841492/
	Peripheral obstruction	↑	https://doi.org/10.1016/j.rmed.2003.09.005; https://doi.org/10.4103/0970-2113.184875; https://doi.org/10.1016/S0140-6736(22)00470-6
	Reactance area	↑	https://doi.org/10.4103/0970-2113.184875; https://doi.org/10.1016/S0140-6736(22)00470-6
	Residual volume	↑	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/
	Tidal volume (acute)	↑	https://doi.org/10.1042/cs0610085; https://doi.org/10.1152/jappl.1985.58.6.1975
	Total lung capacity	↓	https://pmc.ncbi.nlm.nih.gov/articles/PMC3229853/
	Vital capacity	↓	https://pubmed.ncbi.nlm.nih.gov/12841492/

Metabolic syndrome	Apolipoprotein A1	↓	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1161/CIRCULATIONAHA.104.482570
	Apolipoprotein B	↑	https://doi.org/10.1161/CIRCULATIONAHA.104.482570
	Blood glucose	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008
	Hemoglobin glycosylated	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1080/1354750X.2017.1419284
	High-density lipoprotein cholesterol	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1016/j.jacl.2009.10.008
	Low-density lipoprotein cholesterol	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1016/j.jacl.2009.10.008
	Total cholesterol	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008
	Triglycerides	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1016/j.jacl.2009.10.008
Oral health	Bleeding on probing	↑	https://doi.org/10.2196/15350
	Clinical Attachment Loss	↑	https://doi.org/10.2196/15350
	Periodontal pocket depth	↑	https://doi.org/10.2196/15350
	Gingival inflammation	↑	https://doi.org/10.2196/15350
	Olsenella uli	↑	https://doi.org/10.1177/0022034515590581; https://doi.org/10.1186/s12941-022-00499-2
	Plaque control record	↑	https://doi.org/10.2196/15350
	Porphyromonas gingivalis	↑	https://doi.org/10.1111/omi.12273; https://doi.org/10.1016/j.disamonth.2011.03.008
	Pseudoramibacter alactolyticus	↑	https://doi.org/10.1177/0022034515590581; https://doi.org/10.1038/ismej.2014.114
	Tannerella forsythia	↑	https://doi.org/10.1038/s41598-020-80937-3; https://doi.org/10.3389/froh.2021.751099
	Tooth mobility	↑	https://doi.org/10.2196/15350
	Treponema denticola	↑	https://doi.org/10.1038/s41598-020-80937-3; https://doi.org/10.3389/froh.2021.751099
Oxidative stress	8-epi-prostaglandin F2alpha	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	8-hydroxy-2'-deoxyguanosine	↑	https://doi.org/10.1080/10590500902885684; https://doi.org/10.1089/ars.2015.6508; https://doi.org/10.1093/carcin/18.9.1763; https://doi.org/10.3390/ijerph6020445
	8-iso-prostaglandin F2alpha	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	H2O2 breakdown activity	↓	https://doi.org/10.3390/antiox11091829
	H2O2 production	↑	https://doi.org/10.3390/antiox11091829
	Malondialdehyde	↑	https://doi.org/10.7759/cureus.60629
	Myeloperoxidase	↑	https://doi.org/10.1080/1354750X.2017.1419284; https://doi.org/10.1161/01.ATV.0000163262.83456.6d
	Protein carbonyls	↑	https://doi.org/10.1089/ars.2009.2887; https://doi.org/10.1016/j.cbi.2024.111008
	Soluble Nox2-derived peptide	↑	https://doi.org/10.1016/j.chest.2016.04.012
	Total anti-oxidant capacity	↓	https://doi.org/10.5114/pja.2022.116285; https://doi.org/10.1186/1475-2891-6-39
	Vitamin E	↓	https://doi.org/10.2147/CIA.S158513

Platelet function & activation	11-dehydrothromboxane B2	↑	https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1080/1354750X.2017.1419284
	Atheroma-chip, area under the curve	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Atheroma-chip, time to reach 10 kPa	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Atheroma-chip, time to reach occlusion pressure	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Fibrinogen	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1080/1354750X.2017.1419284
	Platelet count	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.3109/08958378.2015.1013227
	Platelet-chip, area under the curve	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Platelet-chip, time to reach 10 kPa	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Platelet-chip, time to reach occlusion pressure	↓	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.1007/s12012-023-09802-9
	Platelet-derived extracellular vesicles	↑	https://doi.org/10.1111/jch.14479; https://doi.org/10.1164/rccm.201012-2061OC
	P-selectin expressing extracellular vesicles	↑	https://doi.org/10.1093/ntr/ntx273
	Soluble CD40 ligand	↑	https://doi.org/10.1161/CIRCULATIONAHA.104.482570; https://doi.org/10.1152/ajplung.00074.2015
	Soluble P-selectin	↑	https://doi.org/10.1093/ntr/ntx273; https://doi.org/10.3109/08958378.2015.1013227; https://doi.org/10.1080/1354750X.2017.1419284

Supplementary Figure 1. PRISMA flow diagram for study selection. Abbreviations: HTP = heated tobacco; BoPH = biomarkers of potential harm; AE = adverse events.



Supplementary Table 2. Risk of bias judgements and support for judgements for each included study.

ISRCTN13439529		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"The order of use will be assigned by a pre-defined computer-generated randomisation schedule"
Allocation concealment	Unclear	"In ascending order of subject number, enrolled participants were assigned to receive the four study products in accordance with the pre-defined randomisation sequences, with an equal proportion of participants in each sequence"
Blinding of participants and personnel	High	"open-label" (Trial Reg & Poster). One active (NRT) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"open-label" (Trial Reg & Poster). Primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition 0% in all study groups. Exclusion: 23% of subjects excluded from analysis, "Seven subjects were excluded from the PK analysis population due to major protocol deviations (washout problem)"
Selective reporting	Low	All outcomes listed in the study protocol were fully reported on in at least one literature source
ISRCTN14301360/ UMIN000024988		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"The randomisation will be performed by Covance"
Allocation concealment	Low	"The randomisation will be performed by Covance and the clinics will enrol the participants and assign them to interventions"
Blinding of participants and personnel	High	"open-label" (Trial Reg & JA protocol). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Overall attrition = 1.1%. No subjects who completed the study were excluded from the primary analyses.
Selective reporting	High	There were several outcomes listed in the protocol, namely biomarkers of effect and pharmacokinetic measures, that were not reported on.
ISRCTN80651909		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"The randomization will be computer-generated using SAS Version 9.3"
Allocation concealment	Low	"A randomisation scheme was provided for the clinical site to recruit 30 participants for each arm, giving a total of 150 participants"
Blinding of participants and personnel	High	"open-label" (Trial Reg & JA). Two active (Cess & EC) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"open-label". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=3.45%, overall=3.38%. Exclusion: Glo=6.67% CC=0% EC=6.67% Cess=0% HTP=N/A, overall=3.34%.
Selective reporting	High	No data reported for an entire study arm (C:

		"switching to a non-BAT commercial product"). No quantitative data reported for two biomarker of effect outcomes (WBC count & 8-epi-PGF2α Type III). No data reported for pharmacokinetic outcomes measured
ISRCTN81075760		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"randomised using blocks of computer-generated random number sequences"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"This study will not be blinded" (Protocol supplementary file, pg 26) Cigarette and non-smoker arms were non-active and subjects in the cessation arm received additional levels of support and products to aid smoking abstinence.
Blinding of outcome assessment	Low	"This study will not be blinded". All primary outcomes objectively measured.
Incomplete outcome data	Unclear	Number of participants randomised/enrolled, withdrawn and included in analyses vary between the 90-day, 180-day and 360-day reports. Entire arm (Group C) also removed. It is unclear when this group was removed from the study, why or how many participants were in the group.
Selective reporting	High	Several outcomes listed in the trial registration and protocol have not been reported on in any publications, including one of the primary endpoints, Augmentation index.
Dalrymple, 2022		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	N/A	Cochrane RoB tools designed to assess trials in which the unit of randomisation is people, rather than multiple sites on one individual, selection bias cannot be fairly assessed using this tool on this study.
Allocation concealment	N/A	
Blinding of participants and personnel	Unclear	There is insufficient information provided in the text regarding blinding. One active (EC) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	No information is provided in the text regarding blinding, but all primary outcomes objectively measured.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
UMIN000017297		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Beyond stating the study was 'randomised', no further information provided.
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"Blinding: Open -no one is blinded" (trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Blinding: Open-no one is blinded". All primary outcomes were objectively measured.
Incomplete outcome data	Low	All subjects randomised completed the study and were included in the analyses.
Selective reporting	Low	3 safety profile parameters were not reported, but

		adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source.
UMIN000025777		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Beyond stating the study was 'randomised', no further information provided.
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"Blinding: Open -no one is blinded" (trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Blinding: Open-no one is blinded". All primary outcomes were objectively measured.
Incomplete outcome data	Low	All subjects randomised completed the study and were included in the analyses.
Selective reporting	Low	3 safety profile parameters were not reported, but adverse events data were reported. All other outcomes listed in the methods and on the trial registration are reported on in at least one literature source.
UMIN000041539		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme."
Allocation concealment	Low	"Subjects were randomly assigned to one of six study groups using the electric data capture system and the investigators and site staffs were blinded to the randomization scheme."
Blinding of participants and personnel	High	"Open -no one is blinded". Included non-active comparator (cigarettes).
Blinding of outcome assessment	Low	"Open -no one is blinded". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IT2.0a= 0% DT2.2a= 6.25% THP= 12.5% THS= 6.25% SS= 0% CC= 0%, overall= 4.3%. All completed participants included in analyses.
Selective reporting	Low	All outcomes listed in the study protocol were fully reported on in at least one literature source
NCT02641587		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Allocation concealment	Low	"subjects will be randomized using an interactive web and voice response system (IxRS)"
Blinding of participants and personnel	High	"Masking: None (Open Label)" Trial reg. No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=5% CC=2.5%, overall=4.17%. Exclusion: IQOS=3.75% CC=12.5%, overall=6.6%.
Selective reporting	High	"Samples for 4-HNE analysis have been collected but will not be analyzed due to the failure to develop a selective and quantitative assay." QSU, Intent to Use of CHTP 1.2, Prochaska "Stage of Change" Questionnaire, MCEQ, and pre- and post-bronchodilator FVC, FEV1/FVC,

		FEF 25-75 were not reported in any literature sources.
NCT01959607		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."
Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System."
Blinding of participants and personnel	High	"This was an open-label study; therefore the subjects and investigators were unblinded to subjects' sequence." No supportive products or behavioural support were provided to any participants during the trial, but in one arm the comparator intervention was non-active (cigarettes).
Blinding of outcome assessment	Low	"This was an open-label study". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=5%, IQOS-NRT=0%. No participants who completed the trial were excluded from the analyses.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT02503254		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"subjects were randomized by an interactive web and voice response system"
Allocation concealment	Low	"subjects were randomized by an interactive web and voice response system"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition and exclusion both 0%.
Selective reporting	High	Several outcomes listed in the study protocol were not reported on in the main results article. Only one was reported on in a poster instead.
NCT01967719		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to each product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (NRT) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=0%, overall=3.23%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01989156		
Bias	**Authors' judgements**	**Support for judgement**

Random sequence generation	Low	"randomization was done through the Interactive Web and Voice Response System (IWRS)"
Allocation concealment	Low	"randomization was done through the Interactive Web and Voice Response System (IWRS)"
Blinding of participants and personnel	High	"This is an open-label study; therefore, the subjects and Investigators will be unblinded to subject's arm" (Study protocol) The level of support given to each arm differed: "All subjects in the SA arm will receive smoking cessation counselling and will be able to use nicotine replacement therapy (NRT) if considered necessary by the Investigator or requested by the subject"
Blinding of outcome assessment	Low	"This is an open-label study". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=9%, CC=15%, SA=21%. Although the primary analysis used per-protocol populations, results data for the full analysis set were also provided in the clinical study report.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01970982		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"randomization was performed through an Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was performed through an Interactive Web and Voice Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=0% CC=0% Cess=5%, overall=1.25%. All subjects who completed the study were included in the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01959932		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"randomization was done through an Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was done through an Interactive Web and Voice Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=1.25% CC=0% Cess=0%, overall=0.62%. All subjects who completed the study were included in the analysis.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01780714		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Beyond stating the study was 'randomised', no further information provided.
Allocation concealment	Unclear	No information provided.

Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial and no participants were excluded from the analysis.
Selective reporting	High	Data for 4 outcomes listed in the protocol (Cytochrome P450 2A6 activity, Questionnaire of Smoking Urges, Minnesota Nicotine Withdrawal Scale, Respiratory symptoms) were not reported.
NCT02396381		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization was done through the interactive voice and web response system (IXRS)"
Allocation concealment	Low	"Randomization was done through the interactive voice and web response system (IXRS)"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured
Incomplete outcome data	Low	Attrition: IQOS=15.16% CC=10.69%, overall=2.91%. Although not the main analysis population, full analysis set (as randomised) results data were also presented in the published literature.
Selective reporting	Low	All outcomes reported on in at least one literature source.
NCT01970995		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"randomization was performed through the Interactive Web and Voice Response System"
Allocation concealment	Low	"randomization was performed through the Interactive Web and Voice Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (Cess) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS=2.56% CC=2.38% Cess=5%, overall=3.12%. Exclusion: IQOS=10.26% CC=2.4% Cess=7.5%, overall=7.5%.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT02466412		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization to product exposure sequence will be done through IxRS"
Allocation concealment	Low	"Randomization to product exposure sequence will be done through IxRS"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition was 0%. Exclusion: mCHTP-mCC=4.16% mCC-mCHTP=0%, overall=2.1%
Selective reporting	High	Only results data for the two primary outcomes have thus far been published.

NCT02649556		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Allocation concealment	Low	"Randomization was done during the original study at V4 through the interactive voice and web response system (IXRS)."
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	High	Attrition rates in all arms were <50% (IQOS=8%, CC=9%) and differed by <20%. However results data reported are based on participant product use not randomisation. True ITT or FAS sets were not provided
Selective reporting	High	Several outcomes listed in the study protocol have not been reported on in any publications.
Other	High	Only reported data grouped by participant product use not randomisation.
NCT01967732		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was performed through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial Reg). One active (NRT) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS/CC=4.55% IQOS/NRT=5.56%, overall=4.84%. Exclusion: IQOS/CC=6.81% IQOS/NRT=5.5%, overall=6.45%.
Selective reporting	Low	All outcomes reported in at least one literature source.
NCT01780688		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization was performed using an Interactive Web Response System"
Allocation concealment	Low	"Randomization was performed using an Interactive Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.
NCT01967706		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and

		Web Response System"
Allocation concealment	Low	"Randomization to product exposure sequence was done through an Interactive Telephone and Web Response System"
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). 1 active (NRT) and 1 non-active (CC) comparator
Blinding of outcome assessment	Low	"Masking: None (Open Label)". All primary outcomes objectively measured.
Incomplete outcome data	Low	Attrition: IQOS-CC=2.27% IQOS-NRT=0%, overall=1.61%. No subjects who completed the study were excluded from the analysis.
Selective reporting	Low	All outcomes reported on in at least one literature source.
NCT03364751		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Allocation concealment	Low	"Randomization will be done through the Interactive Web and Voice Response System (IXRS)"
Blinding of participants and personnel	High	"Masking: Single (Investigator)" (trial reg). No active comparator (CC)
Blinding of outcome assessment	Low	"Masking: Single (Investigator)". Primary outcome objectively assessed.
Incomplete outcome data	Low	Attrition: IQOS=1.15% CC=1.18%, overall=1.16%. Exclusion: IQOS=19.54% CC=1.18%, overall=1.74%.
Selective reporting	High	Results data from "Full transcriptomics profile assessment of buccal swabs derived from the right and left buccal mucosa (3 and 6 months)" has not been reported
Other	High	Only reported data grouped by participant product use not randomisation.
DRKS00012919		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Beyond stating the study was 'randomised', no further information provided.
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	"partly double-blinded": Only two interventions/arms were blinded (EC+/EC-). Two active (EC+ & EC-) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	Only the e-cigarette arms were blinded. All primary outcomes objectively measured.
Incomplete outcome data	Unclear	In the protocol the target for enrolment was 55. It is unclear whether 55 completed the study and only 20 were included in the analyses.
Selective reporting	High	In the trial registration, the authors state outcomes relating to "endothelial dysfunction and inflammatory markers" were measured. No specific measures were given and no relevant data were reported.
NCT03301129		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"The randomization list was computer generated"
Allocation concealment	Unclear	No information provided.

Blinding of participants and personnel	Unclear	Despite describing the trial as "Double" blinded on the trial registration, only "Investigator" and "Outcome Assessor" are noted as being masked, not participants.
Blinding of outcome assessment	Low	"Masking: Double (Investigator, Outcomes Assessor)". Primary outcomes were objectively measured
Incomplete outcome data	Low	The 30 subjects excluded were excluded pre-randomisation. No subjects who were randomised withdrew or were excluded from the final analysis population.
Selective reporting	Low	All outcomes reported on in at least one literature source.
NCT03435562		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Order of the products used in each session will be assigned using Latin-square order procedure"
Allocation concealment	Unclear	No information provided.
Blinding of participants and personnel	High	Masking: None (Open Label) (trial reg). 1 active (EC) and 1 non-active (CC) comparators
Blinding of outcome assessment	Low	"Masking: None (Open Label)". Primary outcome objectively measured.
Incomplete outcome data	Low	Overall attrition = 18.18%. All participants who completed the study were included in the analysis.
Selective reporting	High	Results data for heart rate and blood pressure have not been reported.
NCT03452124		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Randomization was performed by an attending research nurse using a table of random numbers as reproduced from the online randomization software http://www.graphpad.com/quickcalcs/index.cfm"
Allocation concealment	Unclear	There is insufficient information provided to determine whether intervention allocation was concealed
Blinding of participants and personnel	Unclear	Trial registration states "Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)", but in the publication the only blinding described is in regard to outcome assessors.
Blinding of outcome assessment	Low	"examinations were executed by a single, blindedto-treatment and to values of measured biomarkers, operator". Outcomes were physiological measures.
Incomplete outcome data	Low	All participants completed the study and none withdrew.
Selective reporting	High	Not all outcomes measured were reported on.
Ioakeimidis, 2021		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Whether or how participants were randomised is unclear.
Allocation concealment	Unclear	How interventions were allocated is not described.
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. Non-active (CC) comparator.
Blinding of outcome assessment	Low	Outcomes were physiological measures.

Incomplete outcome data	Unclear	The authors state they "studied 22 current smokers" but it is unclear whether more than 22 were initially randomised or enrolled.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
Lopez, 2016		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Participants completed each of the three, Latin-square ordered, ~2.5-h sessions" (JA)
Allocation concealment	Unclear	There is no information provided to determine the presence or level of intervention allocation concealment
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. One active (EC) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	No information is provided in the text regarding blinding. Primary outcomes were objectively measured.
Incomplete outcome data	Low	Overall attrition = 37.5%. No subjects who completed the study were excluded form the analysis.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
Yaman, 2021		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Participants were already IQOS users. It is unclear how participants were randomised to CC or HTP.
Allocation concealment	Unclear	Staff asked participants to use products, ie. They were aware. It is not clear if the order of interventions was randomised.
Blinding of participants and personnel	Unclear	No information is provided in the text regarding blinding. Non-active (CC) comparator.
Blinding of outcome assessment	Low	Outcomes were physiological measures.
Incomplete outcome data	Low	Reasons for withdrawal are clearly described.
Selective reporting	Unclear	There was not trial registration or a priori protocol.
NCT06093659		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	High	"Masking: None (Open Label)" (Trial reg). No active comparator (CC).
Blinding of outcome assessment	Low	"Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured.
Incomplete outcome data	Unclear	Number of participants lost to attrition and/or excluded from analyses not reported.
Selective reporting	High	Puff count not reported.
Yuki, 2023		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and	Unclear	There is insufficient information provided in the

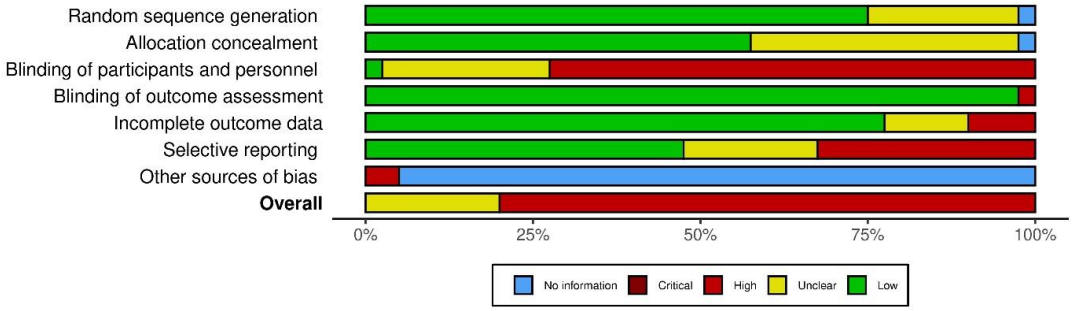
personnel		text regarding blinding. Two active (EC & SA) and one non-active (CC) comparator.
Blinding of outcome assessment	Low	There is insufficient information provided in the text regarding blinding. Primary outcomes objectively measured.
Incomplete outcome data	High	Attrition rates in all arms were <50% (highest 47.1% - Cohort H) but there was a 30.9% difference between the highest and lowest cohorts (Cohort F vs Cohort H).
Selective reporting	Unclear	There was not trial registration or a priori protocol.
UMIN000045304		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"The subjects were randomly assigned into the study groups by using the electronic data capture system, and the investigators and site staff were blinded to the randomization scheme."
Allocation concealment	Low	"The subjects were randomly assigned into the study groups by using the electronic data capture system, and the investigators and site staff were blinded to the randomization scheme."
Blinding of participants and personnel	High	"open-label". Both active and non-active comparators.
Blinding of outcome assessment	Low	"open-label". However all primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition 2% overall, and no participants excluded from analyses.
Selective reporting	Low	All outcomes were reported on.
NCT05459857		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc.
Allocation concealment	Low	Subjects who completed the study screening assessments were assigned a unique randomisation identification number. Subsequently, each subject, based on the identification number, were assigned to use the study products according to one of four product sequences, which were prepared by Celerion, Inc.
Blinding of participants and personnel	High	Masking: None (Open Label) (Trial reg). No active comparator (CC).
Blinding of outcome assessment	Low	"Masking: None (Open Label)" (Trial reg). However all primary outcomes were objectively measured.
Incomplete outcome data	Low	All participants randomised completed the trial and no participants were excluded from the analysis.
Selective reporting	Low	All outcomes were reported on.
NCT05114863		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	The study statistician at the contract research organization generated the random allocation sequence and its implementation.
Allocation concealment	Low	The study statistician at the contract research

		organization generated the random allocation sequence and its implementation.
Blinding of participants and personnel	High	By necessity, this study was unblinded due to the different visual appearances of the study products.
Blinding of outcome assessment	Low	"Masking: None (Open Label)" (Trial reg). Primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition 8% overall, and no participants excluded from analyses.
Selective reporting	Low	All outcomes were reported on.
DRKS00020446		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	Unclear	No details provided regarding blinding. Both active and non-active comparators.
Blinding of outcome assessment	Low	No details provided regarding blinding. However outcomes were objectively measured.
Incomplete outcome data	Unclear	17 participants included, but details of how many were recruited was not reported.
Selective reporting	Unclear	The outcomes listed on the trial registration were not reported on in the publication. It appears the registration may have been for a different study.
ChiCTR2200065055		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Low	"Eligible participants were randomized through a computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4."
Allocation concealment	Low	"Eligible participants were randomized through a computer-generated sequence utilizing a simple randomization algorithm in SAS version 9.4."
Blinding of participants and personnel	High	"Given the open-label nature of the trial, both investigators and participants were cognizant of group assignments. However, the statistical analysts were blinded during data analysis." Non-active comparator (CC)
Blinding of outcome assessment	Low	"open-label". However all primary outcomes were objectively measured.
Incomplete outcome data	Low	Attrition rates in all arms were <50% (HTP=0%, CC=0%) and differed by <20%. All participants included in analyses
Selective reporting	Low	All outcomes were reported on.
Lyytinen, 2024		
Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	Unclear	No details provided regarding blinding. One active comparator (no exposure), but not similar intensity.
Blinding of outcome assessment	Low	No details provided regarding blinding. However outcomes were objectively measured.
Incomplete outcome data	Low	The authors note that due to a loss of data, they had to recruit an additional 8 individuals. All but one of the 32 (original 24 + 8) participants randomised completed the study (attrition 4%).

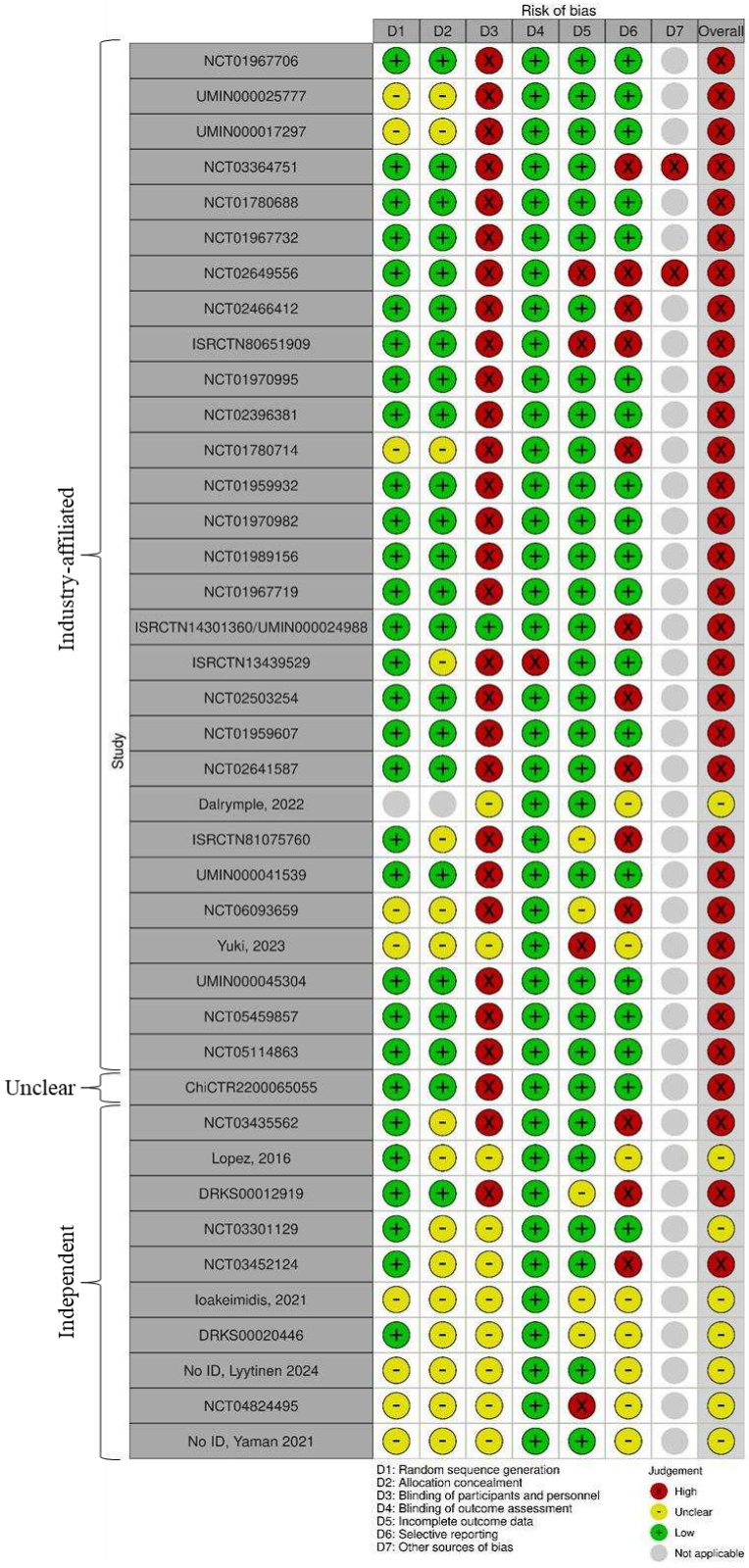
		"23 individuals completed the arterial stiffness analysis and 22 the T-TAS analysis" (exclusion <30%).
Selective reporting	Unclear	There was not trial registration or a priori protocol.

Bias	**Authors' judgements**	**Support for judgement**
Random sequence generation	Unclear	Participants "randomised" but no details of method.
Allocation concealment	Unclear	Participants "randomised" but no details of method.
Blinding of participants and personnel	Unclear	"All statistical analyses were conducted by an investigator who was blinded to the group allocations." But otherwise no further details given regarding blinding. One active comparator (no exposure), but not similar intensity.
Blinding of outcome assessment	Low	Insufficient details provided regarding blinding. However outcomes were objectively measured.
Incomplete outcome data	High	24 enrolled & randomised. 23 included in analyses, unclear if missing one was due to withdrawal or exclusion. A further participant was also excluded from analyses due to being an "outlier".
Selective reporting	Unclear	The outcomes listed on the trial registration were not reported on in the publication. It appears the registration may have been for a different study.

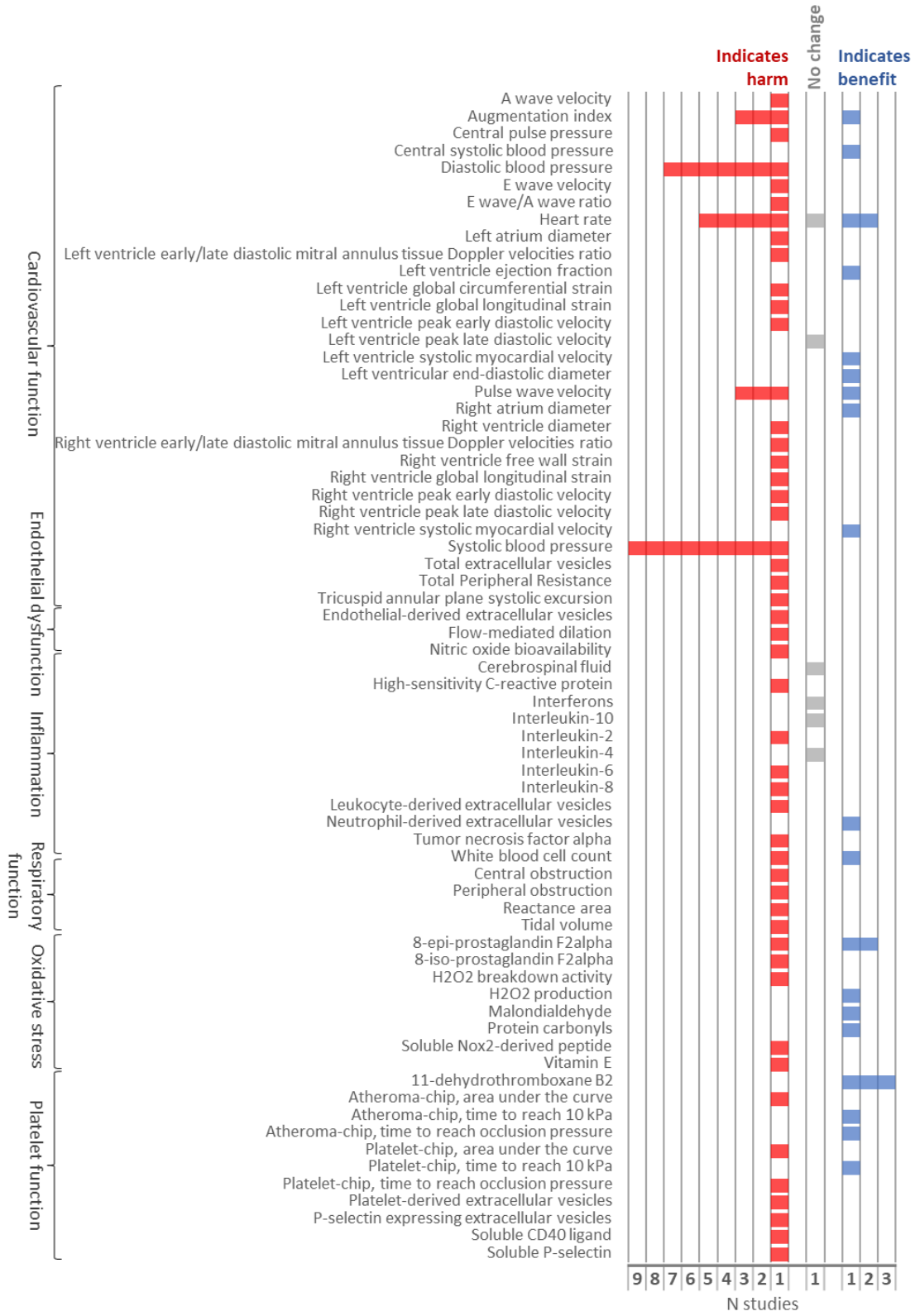
Supplementary Figure 2. Summary plot showing risk of bias judgements across studies.



Supplementary Figure 3. Risk of bias traffic light plot: review authors' judgments about risk of bias items for each included study.

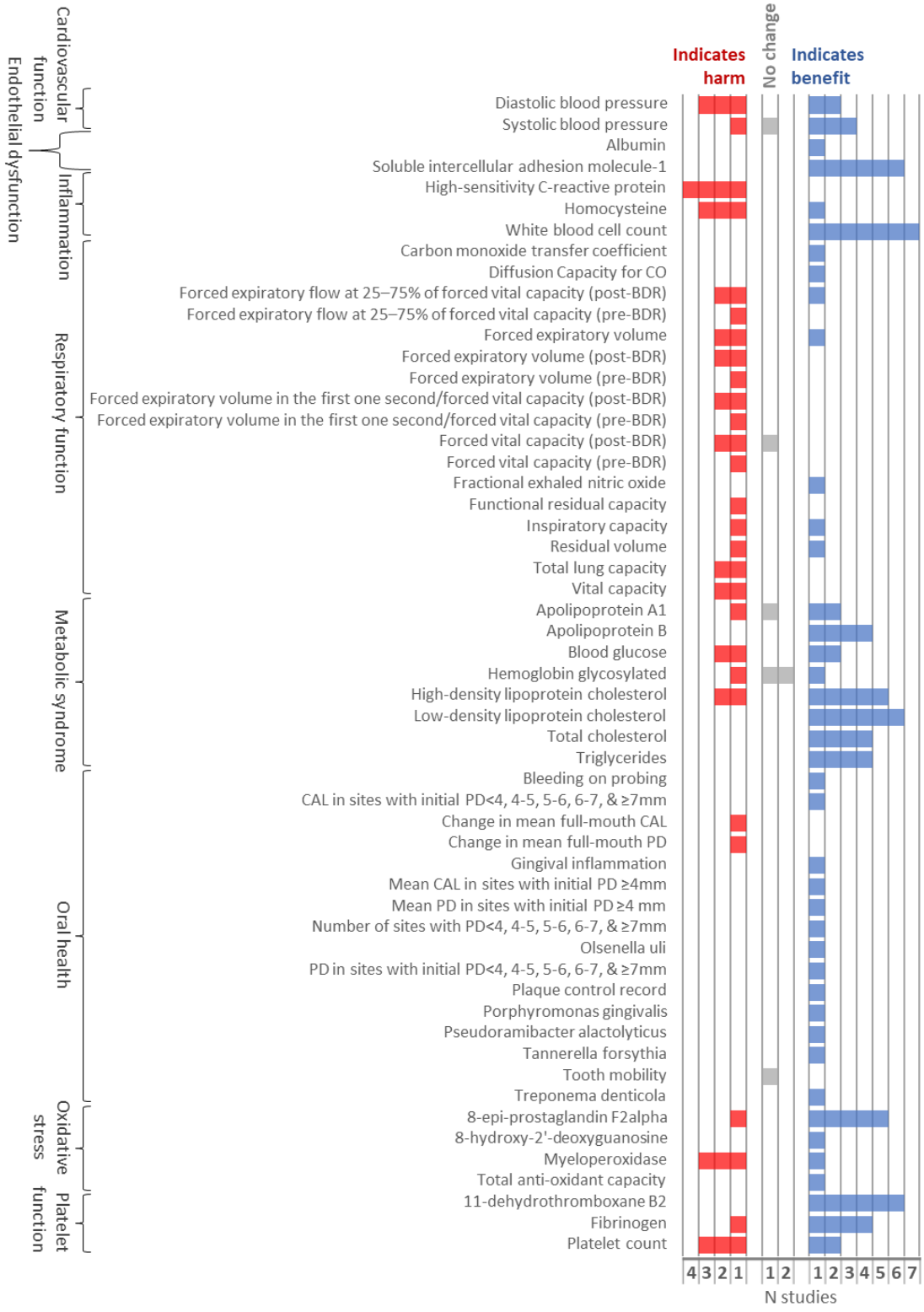


Supplementary Figure 4. Direction of effect between baseline and last follow-up in HTP arms in confined studies.



Supplementary Figure 5. Direction of effect between baseline and last follow-up in HTP arms in ambulatory studies.

Abbreviations: BDR = bronchodilator response.



Supplementary Table 3. Serious and non-serious adverse event data from crossover trials.

Study	Extracted data
NCT01959607	Format: n (%) subjects; [n] AEs **THS-CC:** AEs= 3 (13.6%) [3] Mild AEs= 2 (9.1%) [2] Moderate AEs= 1 (4.5%)[1] Severe AEs= 0 (0%) SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to NRT= 0 [0] AEs related to study procedures= 0 [0] **CC-THS:** AEs= 3 (13.6%) [5] Mild AEs= 2 (9.1%) [4] Moderate AEs= 1 (5.4%) [1] Severe AEs= 0 [0] SAEs= 0 [0] AEs related to IP= 2 (9.1%) [2] Dysphoria= 1 (4.5%) Hepatic function abnormal= 1 (4.5%) AEs related to NRT= 0 [0] AEs related to study procedures= 1 (4.5%) [3] **THS-NRT:** AEs= 4 (44.4%) [5] Mild AEs= 3 (33.3%) [4] Moderate AEs= 1 (11.1%) [1] Severe AEs= 0 [0] SAEs= 0 [0] AEs related to IP= 1 (11.1%) [1] Dysphoria= 1 (11.1%) AEs related to NRT= 0 [0] AEs related to study procedures= 2 (2.2%) [2] **NRT-THS:** AEs= 1 (11.1%) [1] Mild AEs= 1 (11.1%) [1] Moderate AEs= 0 [0] Severe AEs= 0 [0] SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to NRT= 0 [0] AEs related to study procedures= 0 [0]
NCT01967719	Format: n (%) subjects; [n] AEs **THS2.2-CC:** AEs= 7 (31.8%) [10] SAEs= 0 [0] Severe AEs= 0 [0] AEs related to IP= 2 (9.1%) [3] Headache= 1 (4.5%) Vomiting= 1 (4.5%) Nausea= 1 (4.5%) AEs related to NNS= 1 (4.5%) Sneezing= 1 (4.5%) AEs related to study procedures= 2 (9.1%) [4] **CC-THS2.2:** AEs= 7 (31.8%) [9] SAEs= 0 [0]

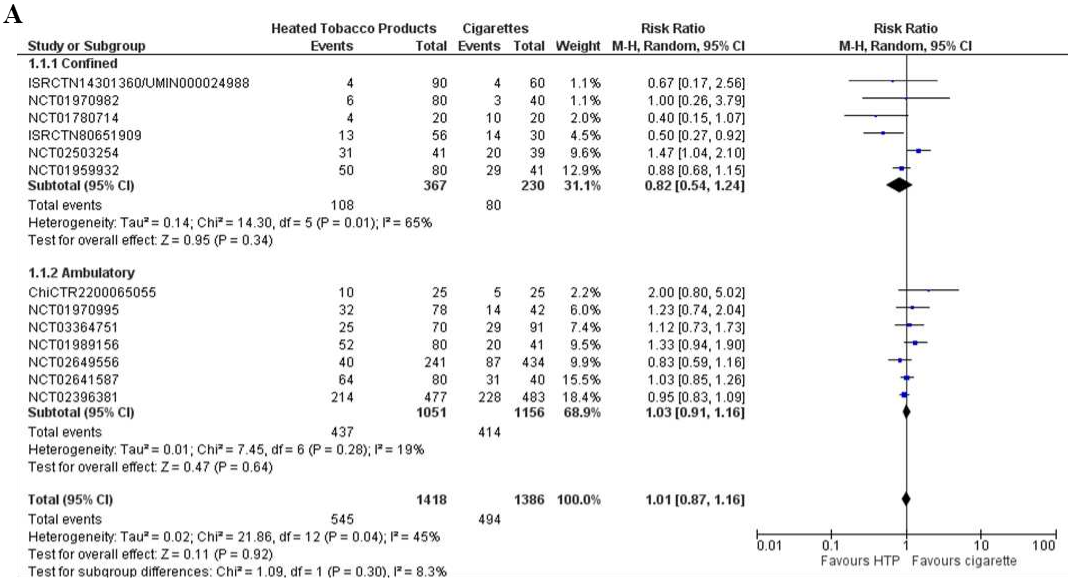
	Severe AEs= 0 [0] AEs related to IP= 1 (4.5%) [1] Vomiting= 1 (4.5%) AEs related to study procedures= 2 (9.1%) [2] **THS2.2-NNS:** AEs= 3 (3.33%) [7] SAEs= 0 [0] Severe AEs= 1 (11.1%) [2] AEs related to IP= 1 (11.1%) [1] Nausea= 1 (11.1%) AEs related to study procedures= 1 (11.1%) [3] **NNS-THS2.2:** AEs= 2 (22.2%) [2] SAEs= 0 [0] Severe AEs= 0 [0] AEs related to IP= 0 [0] AEs related to study procedures= 0 [0]
NCT01967732	Format: n (%) subjects; [n] AEs **THS2.2-CC:** AEs= 10 (45.5%) [21] SAEs= 0 AE related to IP= 4 (18.2%) [4] AE related to study procedure= 3 (13.6%) [7] Mild AE= 7 (31.8%) [18] Moderate AE= 3 (13.6%) [3] Severe AE= 0 Discontinuation due to AE= 0 Dizziness= 5 (22.7%) [6] Headache= 3 (13.6%) [3] Presyncope= 1 (4.5%) [1] Nausea= 2 (9.1%) [3] Vomiting= 1 (4.5%) [1] Muscle spasms= 1 (4.5%) [1] Pallor= 1 (4.5%) [1] Constipation= 1 (4.5%) [1] Dysgeusia= 1 (4.5%) [1] **CC-THS2.2:** AEs= 7 (31.8%) [10] SAEs= 0 AE related to IP= 4 (18.2%) [6] AE related to study procedure= 0 Mild AE= 3 (13.6%) [5] Moderate AE= 4 (18.2%) [5] Severe AE= 0 Discontinuation due to AE= 0 Dizziness= 1 (4.5%) [1] Headache= 2 (9.1%) [2] Presyncope= 3 (13.6%) [3] Nausea= 1 (4.5%) [1] Vomiting= 2 (9.1%) [2] Dysmenorrhoea= 1 (4.5%) [1] **THS2.2-NNS:** AEs= 4 (44.4%) [4] SAEs= 0 AE related to IP= 3 (33.3%) [3]

	AE related to NNS= 0 AE related to study procedure= 0 Mild AE= 2 (22.2%) [2] Moderate AE= 2 (22.2%) [2] Severe AE= 0 Discontinuation due to AE= 0 Headache= 1 (11.1%) [1] Presyncope= 2 (22.2%) [2] Pallor= 1 (11.1%) [1] **NNS-THS2.2:** AEs= 2 (22.2%) [4] SAEs= 0 AE related to IP= 1 (11.1%) [1] AE related to NNS= 0 AE related to study procedure= 0 Mild AE= 1 (11.1%) [3] Moderate AE= 1 (11.1%) [1] Severe AE= 0 Discontinuation due to AE= 0 Dizziness= 1 (11.1%) [1] Muscle spasms= 1 (11.1%) [1] Cough= 1 (11.1%) [1]
NCT01967706	Format: n (%) subjects; [n] AEs **THS-CC:** AEs= 1 (4.5%) [1] SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to study procedure= 0 [0] All AEs were mild. **CC-THS:** AEs= 2 (9.1%) [2] SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to study procedure= 0 [0] All AEs were mild. **THS-NRT:** AEs= 0 [0] SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to study procedure= 0 [0] All AEs were mild. **NRT-THS:** AEs= 1 (11.1%) [1] SAEs= 0 [0] AEs related to IP= 0 [0] AEs related to study procedure= 0 [0] All AEs were mild.
ISRCTN13439529	8 exposure period adverse events (AEs)[3 mild, 5 moderate] were reported by 6 of the 32 subjects (18.8%). One exposure period AE was related to cigarette use (cough with mild severity). The were no severe AEs. 6/23 participants (18.8%) reported 8 mild events (3 mild, 5 moderate). 1 events was related to CC use (cough with mild severity). There were no severe adverse events.
NCT01780688	HTP exposure: 14 participants experienced AEs. Most frequent AEs: nausea

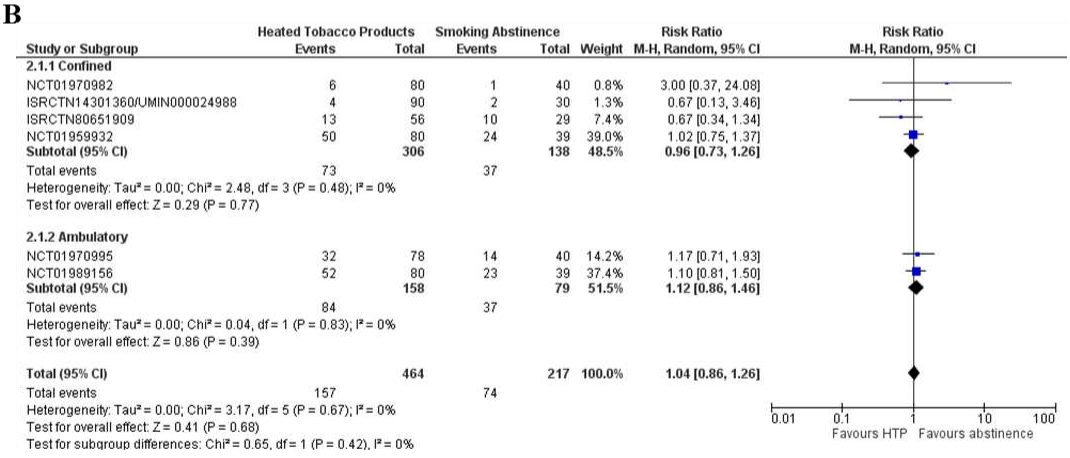
	(4 participants), headache (5), dizziness (4), presyncope (1). CC exposure: 10 participants experienced AEs. Most frequent AEs: nausea (5 participants), headache (2), dizziness (2), presyncope (4), and abdominal pain (2). Most AEs were mild. No AEs were reported by the investigator based on coughing symptoms. No notable changes in spirometry parameters were observed from baseline to the end of the study in either exposure group.
UMIN000017297	HTP arm: 1 participant experienced an AE (vasovagal reaction) after PNTV product use. CC arm: no AE was reported after CC1 smoking. There were no serious AEs reported during the entire study.
NCT05114863	"All product-related adverse events were categorised as mild in severity (e.g., dizziness, nausea and headache)" "No serious product-related adverse events observed following the use of PULZE 2.0 and iD/iSENZIA sticks"
NCT05459857	"During the product trial period on Day −1, during which subjects were allowed to use a single iD of their choice with the Pulze HTS, one mild AE (dizziness) was reported by one (4%) subject. The Investigator considered this event unrelated to study product use. Overall, AEs were infrequently reported in this study, with six AEs reported by five (21%) subjects after study product randomisation. Catheter site pain was reported three times by three (13%) subjects, and the remaining AEs (constipation, dizziness, and neck pain) were reported by one (4%) subject each. The constipation and dizziness events were moderate in severity, and the catheter site pain and neck pain events were mild. The Investigator considered all AEs to be unlikely related or unrelated to study product."
NCT06093659	"Overall, 15 AEs were reported, including eight AEs among six subjects (15.4%) in the non-menthol group and seven AEs among five subjects (13.9%) in the menthol group.

Supplementary Figure 6. Effect of heated tobacco product use compared with cigarette use (A), smoking abstinence (B) and e-cigarette use (C) on rate of participants reporting adverse events.

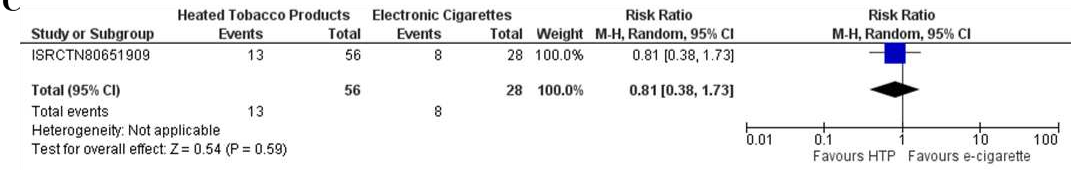
A



B

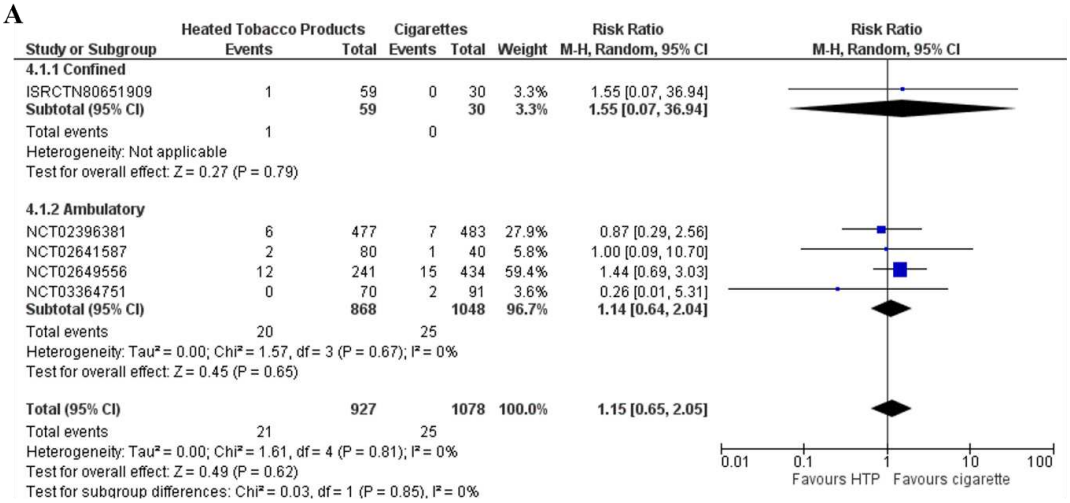


C

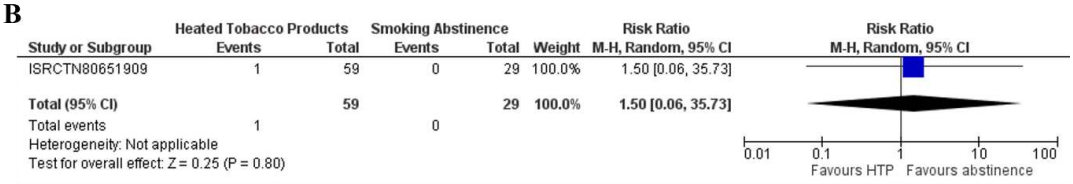


Supplementary Figure 7. Effect of heated tobacco product use compared with cigarette use (A), smoking abstinence (B) and e-cigarette use (C) on rate of participants reporting serious adverse events.

A



B



C