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ORIGINAL RESEARCH

Greenhouse Gas Emissions from Respiratory Treatments: Results from the SABA CARBON International Study

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ABSTRACT

Introduction: Healthcare systems are looking to reduce their carbon impact. Short-acting β_2-agonist (SABA) overuse ($\geq$ 3 canisters/year) is common in asthma and linked to poor outcomes; however, its environmental impact remains unknown. As part of the CARBON programme, this study retrospectively quantified the carbon footprint of SABA and controller inhalers across all respiratory indications and SABA overuse in asthma in lower-middle-income countries (LMICs), upper-middle-income countries and high-income countries across Africa, Asia Pacific, Latin America and the Middle East.

Methods: Two data sources were utilised to evaluate the carbon contribution of inhalers to respiratory care. To quantify greenhouse gas (GHG) emissions associated with total inhaler use across all respiratory indications, inhaler sales data were obtained from IQVIA MIDAS® (Q4/2018–Q3/2019) and compared by dose to prevent confounding from differences in canister actuation counts. GHG emissions associated with SABA overuse in asthma were evaluated

Prior publication: Partial findings from this study were presented at the European Respiratory Society International Congress 2022 (Alzaabi A, Bell J, Montero-Arias F, et al. Carbon footprint of inhalers in respiratory treatment: SABA CARBON International. Eur Respir J. 2022; 60:2901).

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using prescription and self-reported over-the-counter purchase data from the SABA use IN Asthma (SABINA) III study (2019–2020). Inhaler-related GHG emissions were quantified using published data and product life cycle assessments.

Results: SABA accounted for > 50% of total inhaler use and inhaler-related emissions in most countries analysed. The total SABA-related emissions were estimated at 2.7 million tonnes carbon dioxide equivalents, accounting for 70% of total inhaler-related emissions. Among the countries, regions and economies analysed, per capita SABA use and associated emissions were higher in Australia, the Middle East and high-income countries. Most SABA prescriptions for asthma (> 90%) were given to patients already overusing SABA.

Conclusions: Globally, SABA use/overuse is widespread and is the greatest contributor to the carbon footprint of respiratory treatment, regardless of the economic status of countries. Implementing evidence-based treatment recommendations, personalising treatment and reducing healthcare inequities, especially in LMICs, may improve disease control and patient outcomes, thereby reducing SABA overuse and associated carbon emissions beyond SABA use alone.

PLAIN LANGUAGE SUMMARY

The healthcare sector is a large emitter of greenhouse gases (GHGs); therefore, healthcare systems will need to reduce their carbon footprint to meet their carbon reduction targets. In respiratory care, the environmental impact of controller inhalers has received considerable attention due to the global warming potential of the propellants used in metered-dose inhalers. In contrast, little is known about the contribution made by short-acting β_2-agonist (SABA) relievers globally, which are often the only inhaled medication used by many patients with milder asthma. The SABA use IN Asthma (SABINA) programme reported that SABA overuse (3 or more SABA canisters/year) is common and associated with an increased risk of asthma attacks. Since all inhalers have a carbon footprint, SABA overuse may result in an avoidable excess carbon footprint. Therefore, to provide a complete picture of the carbon footprint of respiratory care, we examined the contribution of SABA relievers and their potential overuse. The total SABA-related GHG emissions accounted for 70% of total inhaler-related GHG emissions, and > 90% of prescriptions for SABA relievers for asthma were given to patients who were already overusing their SABA. Overall, SABA use/overuse is commonly observed worldwide and is likely a significant contributor to the carbon footprint of respiratory treatment. Therefore, there is an urgent need for healthcare providers to follow the latest international treatment guidelines to reduce high SABA use in respiratory care and improve patient outcomes. This, in turn, will enable healthcare systems to reduce their carbon footprint from both treatment and patient interactions.

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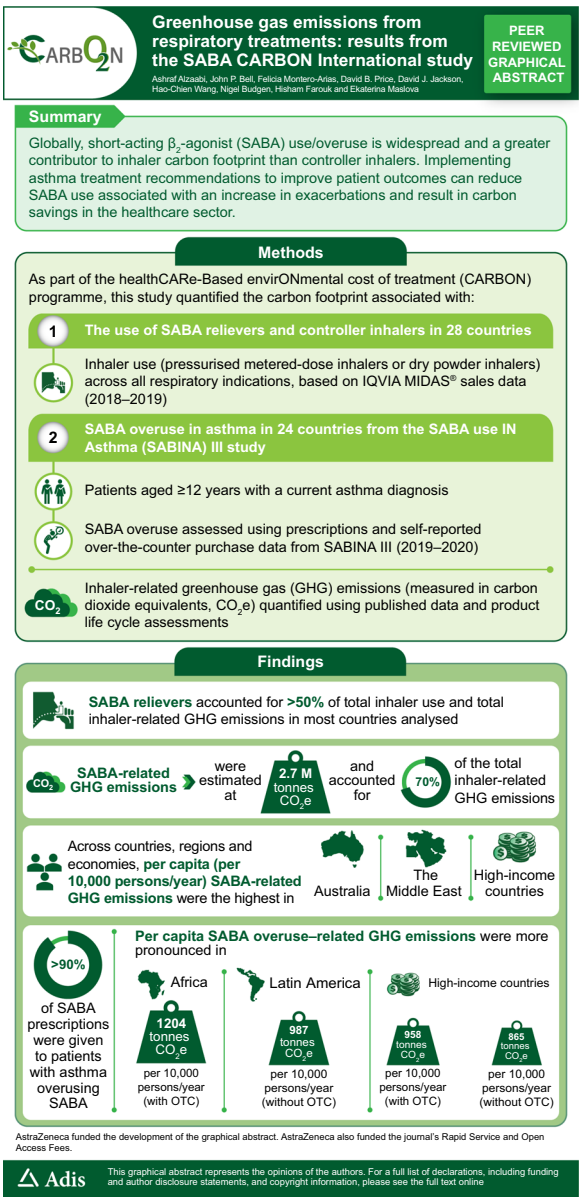
Graphical abstract:



Keywords: Asthma; Asthma control; Carbon footprint; Environmental monitoring; Greenhouse gas emissions; Inhalers; Inhaler therapies; SABA; Short-acting β_2-agonist

Key Summary Points

Why carry out this study?

To date, in respiratory care, the environmental impact of controller inhalers has been the focus of attention due to the high global warming potential of the hydrofluoroalkane propellants used in metered-dose inhalers

However, the contributions of short-acting β_2-agonist (SABA) reliever use, healthcare resource utilisation and other asthma medications to the carbon footprint have not yet been investigated, providing an incomplete picture of the carbon footprint of respiratory care

As part of the healthCARe-Based envirONmental cost of treatment (CARBON) programme, this study quantified the carbon footprint associated with (1) SABA use as a proportion of total inhaler use across all respiratory indications and (2) SABA overuse in asthma in Africa, Asia Pacific, Latin America and the Middle East

What was learned from the study?

Across all respiratory indications, SABA use was high, accounting for > 50% of total inhaler use and inhaler-related greenhouse gas (GHG) emissions in most countries assessed; total SABA-related GHG emissions accounted for 70% of total inhaler-related GHG emissions

Most SABA prescriptions for asthma (> 90%) were given to patients already overusing SABA, placing them at higher risk of a future exacerbation

These findings emphasise the need to implement international recommendations that aim to reduce high SABA use in respiratory care, especially in asthma, and to adopt patient-centric principles to optimise patient outcomes which will also help healthcare systems achieve their carbon reduction targets

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.23899662.

INTRODUCTION

In an effort to tackle the climate crisis, countries are increasingly seeking to decarbonise their economies by establishing carbon reduction targets in accordance with international treaties on climate change, such as the Paris Agreement [1, 2]. The healthcare sector is one of the largest public sector sources of greenhouse gas (GHG) emissions, accounting for 4.6% of global GHG emissions [3]; therefore, it is a key target for decarbonisation. In 2022, over 60 countries committed to build climate-resilient and low-carbon healthcare systems, with over 20 of these countries aiming to achieve 'net zero' carbon emissions from their healthcare systems by 2050 [4]. Approximately 60% of the global healthcare carbon footprint is emitted from countries outside of North America and the European Union [5]. Under-resourced and fragmented healthcare services in lower-middle-income countries (LMICs) are more carbon-intensive in economic terms than those in upper-middle-income countries (UMICs) and high-income countries (HICs), which may be explained in part by inefficient and non-sustainable energy supplies and poor access to care [6]. Thus, to achieve carbon reductions in these healthcare systems, it is imperative to identify tangible targets for decarbonisation that are simple to implement and have a positive impact on patient care.

Despite the availability of effective inhaler therapies, both asthma and chronic obstructive pulmonary disease (COPD) remain poorly controlled among a substantial proportion of patients worldwide [7, 8]. This is particularly evident in LMICs, where access to and affordability of medications are limited, which in turn may foster suboptimal patient management [9, 10]. Inhaled corticosteroids (ICS) and bronchodilators represent the mainstay of respiratory care and are delivered via pressurised metered-dose inhalers (pMDIs) or dry powder inhalers (DPIs) [11]. Medication costs largely influence treatment decisions in many countries. In developing countries where patients are required to purchase medications as an out-of-pocket expense, patients tend to address their acute need for rapid symptom relief rather than long-term asthma control [12]. To date, in respiratory care, the environmental impact of controller inhalers delivered via pMDIs has been the focus of attention [11]. This is due to the global warming potential (GWP) of the hydrofluoroalkane (HFA) propellants used in pMDIs that result in a comparatively higher carbon footprint than DPIs [13]. However, the contributions of short-acting β_2-agonist (SABA) reliever use and other asthma medications to the carbon footprint have not yet been investigated, providing an incomplete picture of the carbon footprint of respiratory care.

Findings from the real-world SABA use IN Asthma (SABINA) programme [14] report widespread SABA overuse (defined as $\geq$ 3 canisters/year) in the UK and other European countries and its link with an increased risk of exacerbations and healthcare resource utilisation (HCRU) [15–17], all of which carry a carbon footprint. Similarly, in SABINA III, which included 24 countries outside of Europe, $\geq$ 3 (versus 1–2) SABA prescriptions/year were associated with lower odds of at least partly controlled asthma and higher rates of severe exacerbations [18]. Evaluating the contribution of controller and SABA inhalers to the carbon footprint of respiratory treatments and the excess carbon footprint associated with SABA inhaler use and overuse globally may help identify targets for decarbonisation in respiratory care. As part of the healthCARe-Based envirONmental cost of treatment (CARBON) programme [19], the SABA CARBON International study quantified the carbon footprint associated with (1) SABA use as a proportion of total inhaler use across all respiratory indications and (2) SABA overuse in asthma in Africa, Asia Pacific, Latin America and the Middle East.

Table 1 List of countries included in the IQVIA and SABINA III [18] analyses stratified by geographical region and gross national income

IQVIA	
Stratification by geographical region	
Asia Pacific	Australia, China, Hong Kong, India, Japan, Kazakhstan, Malaysia, New Zealand, Philippines, Russia, Singapore, South Korea, Taiwan, Thailand, Vietnam
Latin America	Argentina, Brazil, Central America, Chile, Colombia, Mexico, Peru
Africa	Algeria, Egypt, South Africa
Middle East	Saudi Arabia, Turkey, UAE
Stratification by gross national income*	
LMIC	Algeria, Egypt, India, Philippines, Vietnam
UMIC	Argentina, Brazil, Central America, China, Colombia, Kazakhstan, Malaysia, Mexico, Peru, Russia, South Africa, Thailand, Turkey
HIC	Australia, Chile, Hong Kong, Japan, New Zealand, Saudi Arabia, Singapore, South Korea, Taiwan, UAE
SABINA III	
Stratification by geographical region	
Asia Pacific	Australia, India, Indonesia, Malaysia, Philippines, Russia, Singapore, South Korea, Taiwan, Thailand
Latin America	Argentina, Brazil, Chile, Colombia, Costa Rica, Mexico
Africa	Egypt, Kenya, South Africa
Middle East	Gulf (Kuwait, Oman, UAE), Saudi Arabia, Turkey
Stratification by gross national income*	
LMIC	Egypt, India, Indonesia, Kenya, Philippines
UMIC	Argentina, Brazil, Colombia, Costa Rica, Malaysia, Mexico, Russia, South Africa, Thailand, Turkey
HIC	Australia, Chile, Gulf (Kuwait, Oman, UAE), Saudi Arabia, Singapore, South Korea, Taiwan

HIC high-income country, *LMIC* lower-middle-income country, *SABA* SABA short-acting β_2-agonist, *SABINA* SABA use IN Asthma, *UAE* United Arab Emirates, *UMIC* upper-middle-income country, *USD* United States dollar
*Gross national income per capita based on the 2020 World Bank classifications [31]: LMIC, 1046 USD–4095 USD; UMIC, 4096 USD–12,695 USD; HIC, > 12,695 USD

METHODS

Study Design and Population

To evaluate the carbon contribution of SABA and controller medications to respiratory care, this retrospective cohort study utilised two distinct data sources: IQVIA MIDAS® inhaler sales data and data on SABA overuse from the SABINA III study [18].

Inhaler Sales Data from IQVIA MIDAS

An analysis of IQVIA Quarterly MIDAS data MAT Q3 2019 (Q42018–Q3/2019) was

conducted across all respiratory indications in 28 countries (Table 1) for inhaler use pertaining to SABA and controller medications (pMDIs and DPIs). IQVIA MIDAS maintains medication sales and prescription data from over 90 countries, helps understand medication use and tracks prescribing information across countries, representing > 98% of global sales [20]. IQVIA MIDAS data are based on locally captured medication sales and prescription data from a range of supplier types, including retail and hospital pharmacies, wholesalers and manufacturers (Supplementary Materials Fig. S1A). The two major types of data collected by IQVIA include retail and hospital sales data (Supplementary Materials Fig. S1B). Retail data include medication sales and dispensing from retail pharmacies. Hospital sales data measure the level of both purchasing and dispensing by hospital pharmacies. The IQVIA MIDAS inhaler sales data include product name, drug class, device type and actuation count. The inhaler sales data, accessed and analysed using the STAR system (a platform provided by IQVIA), served as a surrogate for their actual use. Controller medications included ICS-containing therapies (ICS, ICS/long-acting β_2-agonists [LABAs], ICS/LABA/long-acting muscarinic antagonists [LAMAs]), LABA, LAMA and LABA/LAMA. Reliever medications other than SABAs were not assessed in this study. Data were compared by dose to limit confounding from differences in canister actuation counts based on the device type (pMDI or DPI). Therefore, a 1:1 equivalence of actuation-to-dose was assumed for SABA and controller medications delivered via a DPI and a 2:1 ratio for actuation-to-dose was assumed for controller medication delivered via a pMDI.

Data on Short-Acting β_2-Agonist Overuse in Asthma from the SABA Use IN Asthma III Study

Retrospective data on SABA overuse in asthma were analysed from the 24 countries participating in the multi-country SABINA III study (2019–2020; Table 1) [18]. SABA overuse in patients with asthma of any severity was assessed using medical records data on prescription and self-reported over-the-counter (OTC) purchase of SABA [18]. Patient eligibility criteria for SABINA III have been described previously [18] (Supplementary Materials).

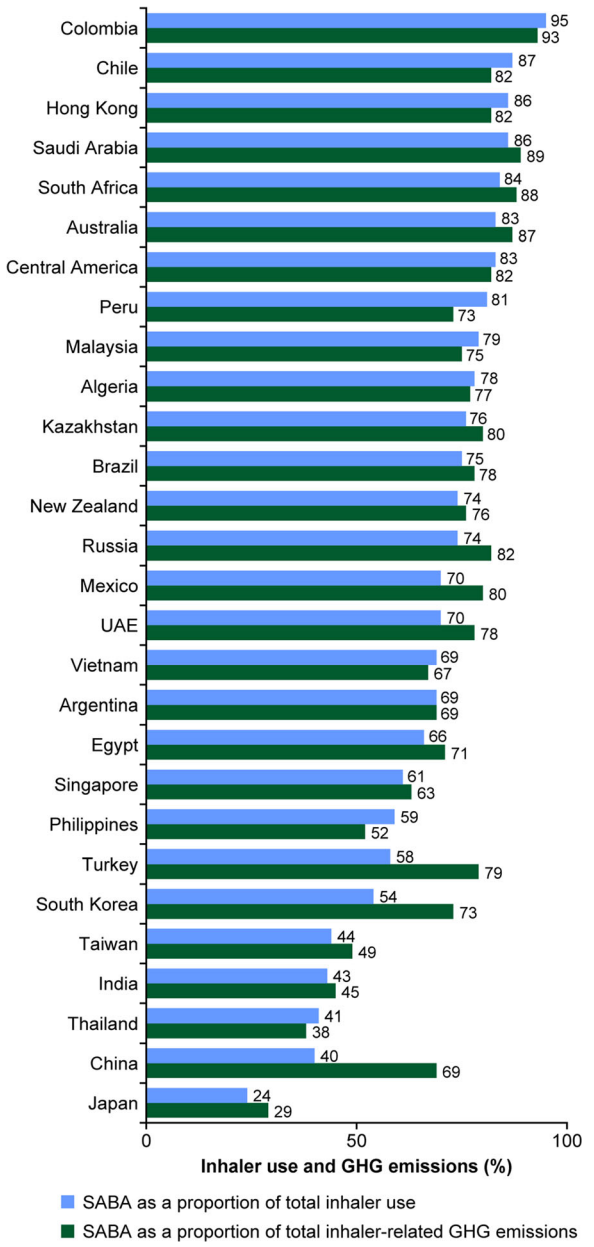


Fig. 1 SABA inhaler use and associated GHG emissions as a proportion of total inhaler use based on sales data from the IQVIA MIDAS data*.*Based on internal analysis by the authors using IQVIA MIDAS® data, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved. Inhaler sales data were used as surrogates for actual use. *GHG* greenhouse gas, *SABA* short-acting β_2-agonist, *UAE* United Arab Emirates

Table 2 Total SABA and controller medication sales and GHG emissions based on the IQVIA MIDAS data* stratified by country, geographical region and gross national income

	Total SABA use (doses × 1000)	Total controller medication use (doses × 1000)	SABA use as a proportion of total inhaler use (%)	Per capita SABA use (doses/ 10,000 persons/ year)	Per capita controller medication use (doses/ 10,000 persons/ year)	Total SABA-related GHG emissions (tonnes CO_2e)	Total controller medication-related GHG emissions (tonnes CO_2e)	SABA-related GHG emissions as a proportion of total inhaler-related GHG emissions (%)	Per capita SABA-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)	Per capita controller medication-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)
Country										
Algeria	1,160,676	333,154	78	260,826	74,866	155,463.9	45,490.1	77	34.9	10.2
Argentina	643,052	293,953	69	146,481	66,960	86,215.3	38,581.1	69	19.6	8.8
Australia	2,674,382	534,967	83	1,157,741	231,587	355,113.6	55,046.7	87	153.7	23.8
Brazil	3,439,628	1,158,963	75	167,134	56,315	461,158.1	132,223.5	78	22.4	6.4
Central America	124,057	26,024	83	6835	1434	16,632.6	3636.8	82	0.9	0.2
Chile	322,681	48,052	87	167,192	24,897	43,262.5	9573.9	82	22.4	5.0
China	547,109	810,365	40	3983	5900	73,262.2	32,280.7	69	0.5	0.2
Colombia	508,470	27,985	95	98,924	5444	68,171.6	5326.8	93	13.3	1.0
Egypt	633,076	333,392	66	60,814	32,026	84,035.2	34,953.1	71	8.1	3.4
Hong Kong	366,219	57,873	86	481,867	76,148	48,937.8	10,863.9	82	64.4	14.3
India	2,913,080	3,784,919	43	22,994	29,875	329,668.0	404,304.4	45	2.6	3.2
Japan	419,570	1,365,030	24	33,115	107,737	53,191.8	130,123.9	29	4.2	10.3
Kazakhstan	164,283	52,256	76	86,465	27,503	22,025.8	5583.8	80	11.6	2.9
Malaysia	565,006	152,218	79	172,785	46,550	75,697.6	25,771.2	75	23.1	7.9

Table 2 continued

	Total SABA use (doses × 1000)	Total controller medication use (doses × 1000)	SABA use as a proportion of total inhaler use (%)	Per capita SABA use (doses/ 10,000 persons/ year)	Per capita controller medication use (doses/ 10,000 persons/ year)	Total SABA-related GHG emissions (tonnes CO_2e)	Total controller medication-related GHG emissions (tonnes CO_2e)	SABA-related GHG emissions as a proportion of total inhaler-related GHG emissions (%)	Per capita SABA-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)	Per capita controller medication-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)
Mexico	406,945	173,532	70	33,031	14,085	54,560.0	13,946.9	80	4.4	1.1
New Zealand	442,680	153,422	74	903,429	313,105	57,986.8	17,999.7	76	118.3	36.7
Peru	62,571	14,411	81	18,734	4315	8389.0	3055.8	73	2.5	0.9
Philippines	193,292	135,476	59	17,429	12,216	22,653.9	20,989.5	52	2.0	1.9
Russia	1,939,497	686,239	74	136,201	48,191	260,032.4	58,555.9	82	18.3	4.1
Saudi Arabia	510,494	86,043	86	181,026	30,512	68,443.0	8572.4	89	24.3	3.0
Singapore	47,981	30,144	61	81,324	51,092	6426.1	3823.6	63	10.9	6.5
South Africa	763,004	142,080	84	140,516	26,166	102,181.6	14,544.0	88	18.8	2.7
South Korea	178,459	152,236	54	35,061	29,909	23,916.0	9030.9	73	4.7	1.8
Taiwan	62,029	77,658	44	26,395	33,046	8315.9	8517.0	49	3.5	3.6
Thailand	178,514	254,163	41	25,502	36,309	23,743.7	39,306.3	38	3.4	5.6
Turkey	1,458,606	1,075,786	58	171,198	126,266	195,558.4	50,844.5	79	23.0	6.0
UAE	67,947	29,075	70	67,947	29,075	9072.6	2596.2	78	9.1	2.6

Table 2 continued

	Total SABA use (doses × 1000)	Total controller medication use (doses × 1000)	SABA use as a proportion of total inhaler use (%)	Per capita SABA use (doses/ 10,000 persons/ year)	Per capita controller medication use (doses/ 10,000 persons/ year)	Total SABA-related GHG emissions (tonnes CO_2e)	Total controller medication-related GHG emissions (tonnes CO_2e)	SABA-related GHG emissions as a proportion of total inhaler-related GHG emissions (%)	Per capita SABA-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)	Per capita controller medication-related GHG emission (tonnes CO_2e/ 10,000 persons/ year)
Vietnam	178,912	80,692	69	18,388	8293	23,987.1	11,706.7	67	2.5	1.2
Geographical region										
Africa	2,556,756	808,625	76	126,011	39,853	341,681	94,987	78	17	5
Asia Pacific	10,871,013	8,327,654	57	32,400	24,819	1,384,959	833,904	62	4	2
Latin America	5,507,404	1,742,918	76	83,636	26,468	738,389	206,345	78	11	3
Middle East	2,037,047	1,190,903	63	165,077	96,507	273,074	62,013	81	22	5
Gross national income[†]										
LMICs	5,079,036	4,667,632	52	31,281	28,747	615,808	517,444	54	4	3
UMICs	10,800,742	4,867,971	69	44,700	20,146	1,447,628	423,657	77	6	2
HICs	5,092,442	2,534,496	67	169,692	84,455	674,666	256,148	72	22	9

CO_2e carbon dioxide equivalent, *GHG* greenhouse gas, *HIC* high-income country, *LMIC* lower-middle-income country, *per capita* per 10,000 persons/year, *SABA* short-acting β_2-agonist, *UAE* United Arab Emirates, *UMIC* upper-middle-income country, *USD* United States dollar

*Based on internal analysis by the authors using IQVIA MIDAS® data, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved

†Gross national income per capita based on the 2020 World Bank classifications [31]: LMIC, 1046 USD–4095 USD; UMIC, 4096 USD–12,695 USD; HIC, > 12,695 USD

Statistical Analysis

All analyses were descriptive. Annual GHG emissions were expressed as carbon dioxide equivalents (CO_2e; supplementary methods). Inhaler use-related GHG emissions were quantified using SimaPro life cycle assessment (LCA) software modelling resource and energy consumption data, Ecoinvent® datasets, certified published studies [13, 21, 22] and modelled estimates and are listed in Supplementary Materials Table S1. Calculations for the carbon footprint considered emissions from the entire life cycle of inhalers, including the manufacture and transport of the inhaler device (e.g. pMDI or DPI), and end-of-life disposal. The study referred to the Intergovernmental Panel on Climate Change Fifth Assessment Report on GWP of HFAs for a 100-year time period to generate product LCAs [23]. A sensitivity analysis confirmed an up to approximately 8% increase in GHG estimates when calculated using updated guidelines, product LCAs and recently published studies [23–28] (Supplementary Materials).

In the analyses performed using IQVIA data, SABA use and associated GHG emissions were presented as a proportion of total inhaler use and total inhaler-related GHG emissions, respectively. Per capita (per 10,000 persons/year) inhaler use and associated carbon footprint were calculated using the national population of each country as derived from the Population Division of the United Nations Website [29]. Total inhaler use based on IQVIA inhaler sales data was presented as doses in thousands (doses $\times$ 1000).

In SABINA III, data on SABA prescriptions were collected using categories of 1–2, 3–5, 6–9, 10–12 and $\geq$ 13 canisters and assessed at category midpoints of 1.5, 4, 7.5, 11 and 13 canisters. All analyses were conducted with and without SABA OTC. The proportion of SABA prescriptions given to patients who were already overusing SABA was examined. This was calculated as SABA prescriptions in patients already overusing SABA as a proportion of the total SABA prescriptions. SABA overuse-related GHG emissions per capita (per 10,000 persons/year) were calculated using the study population. Patients were also stratified based on investigator-classified asthma severity, guided by the Global Initiative for Asthma (GINA) 2017 treatment steps, as having mild (steps 1–2) or moderate-to-severe (steps 3–5) asthma [30].

All results were stratified by geographical regions of Africa, Asia Pacific, Latin America and the Middle East and by gross national income per capita (LMICs, UMICs and HICs) based on the 2020 World Bank classifications [31] (Table 1).

Ethics Approval

The SABINA III study was conducted in compliance with the Declaration of Helsinki, 1964, including its later amendments, and Good Clinical Practice guidelines, and each study site received approval from an institutional review board. Informed consent was obtained from all patients or their legal guardians. Ethics committee approval was not required for accessing data from IQVIA MIDAS.

RESULTS

Analyses Performed Using IQVIA Data

Short-Acting β_2-Agonist and Controller Medication Use

SABA use as a proportion of total inhaler use ranged from 24% (Japan) to 95% (Colombia) and accounted for > 50% of total inhaler use in 23 of the 28 countries analysed (Fig. 1, Table 2). When analysed across regions, SABA use as a proportion of total inhaler use was the highest in Africa (76%) and Latin America (76%; Table 2). From a gross national income perspective, SABA use as a proportion of total inhaler use was higher among UMICs (69%) than among HICs (67%) and LMICs (52%; Table 2).

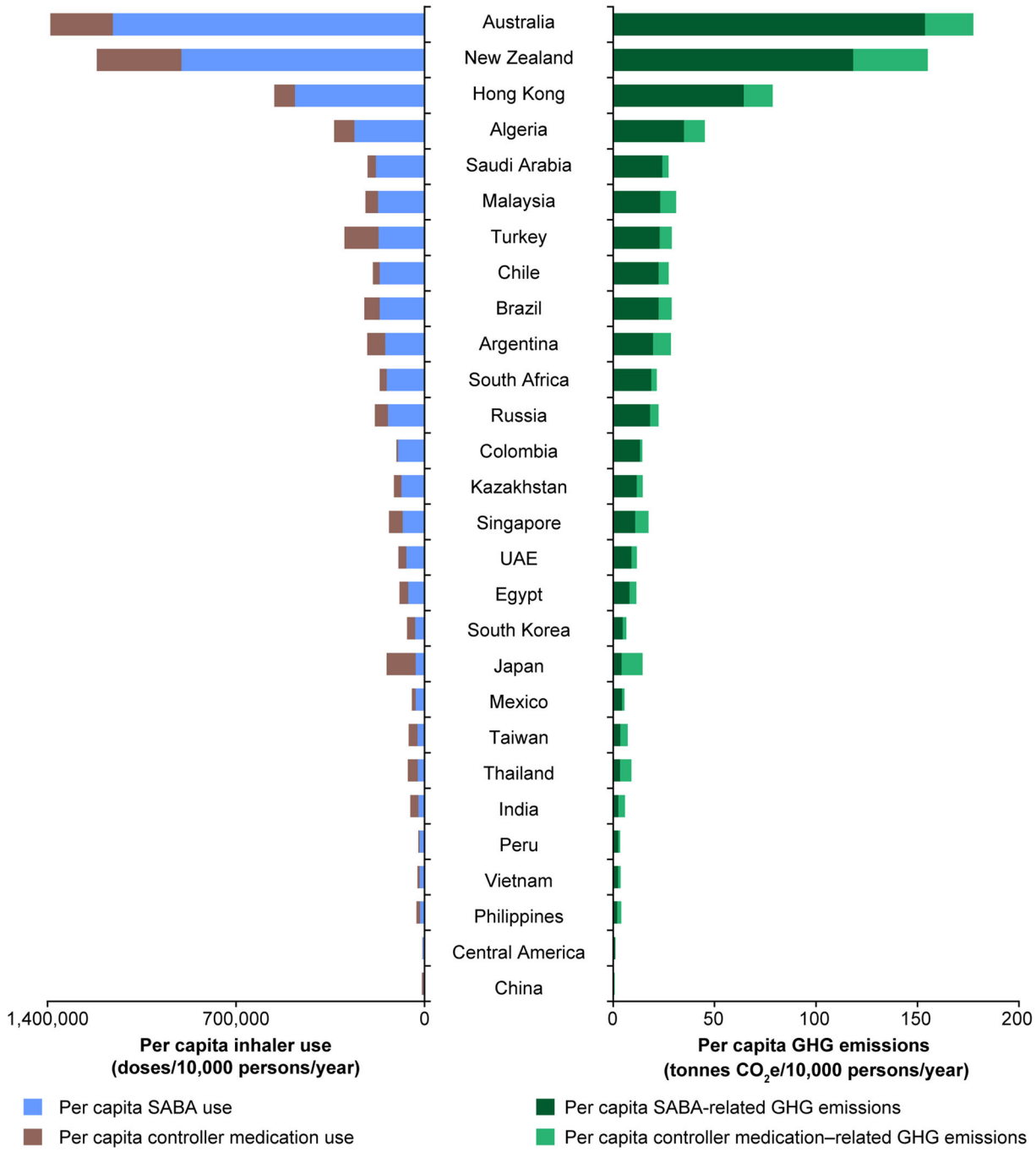


Fig. 2 Per capita SABA and controller medication use and associated GHG emissions based on the IQVIA MIDAS sales data*.*Based on internal analysis by the authors using IQVIA MIDAS® data, reflecting estimates of real-world activity. Copyright IQVIA. All rights reserved. Inhaler sales data were used as surrogates for actual use. *CO_2e* carbon dioxide equivalent, *GHG* greenhouse gas, per capita per 10,000 persons/year, *SABA* short-acting β_2-agonist, *UAE* United Arab Emirates

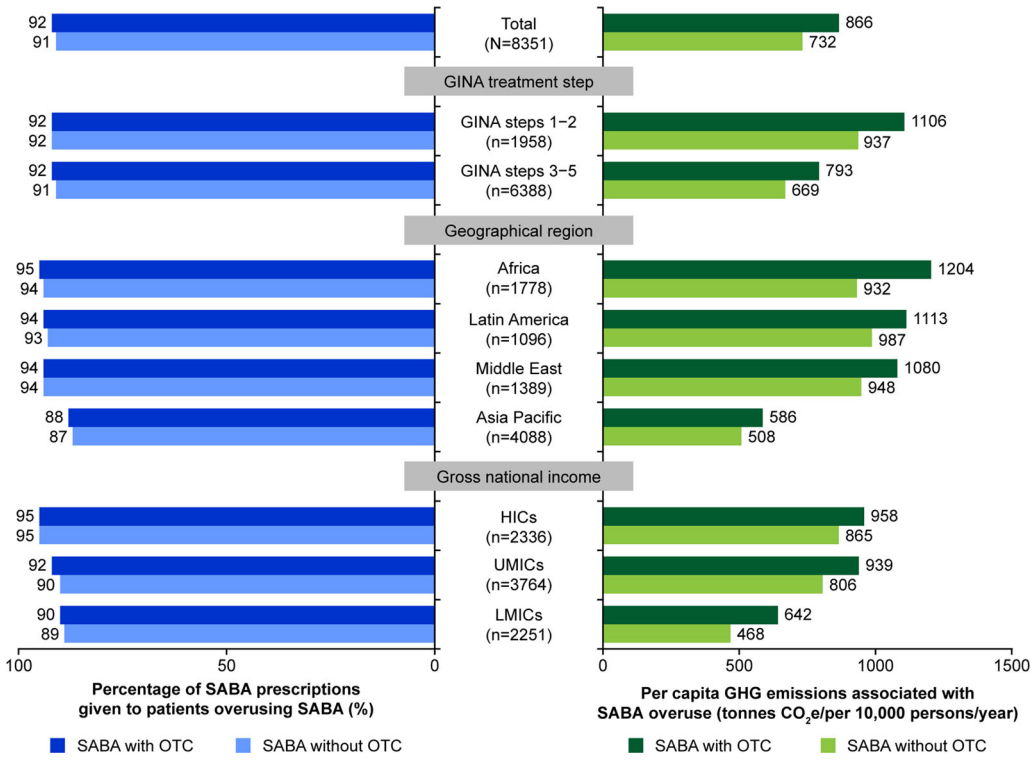


Fig. 3 Proportion of SABA prescriptions given to patients overusing SABA (left) and per capita GHG emissions associated with SABA overuse* (right) based on prescription data in patients with asthma from the SABINA III cohort† [18] stratified by GINA treatment step, region and gross national income‡.*SABA overuse is defined as use of ≥ 3 SABA canisters/year. Inhaler prescription data were used as surrogates for actual use.†Based on internal analysis by the authors using data from the SABINA III cohort. ‡Gross national income per capita based on the 2020 World Bank classifications [31]: LMIC, 1046 USD–4095 USD; UMIC, 4096 USD–12,695 USD; HIC, > 12,695 USD. *CO_2e* carbon dioxide equivalent, *GHG* greenhouse gas, *GINA* Global Initiative for Asthma, *HIC* high-income country, *LMIC* lower-middle-income country, *OTC* over the counter, *per capita* per 10,000 persons/year, *SABA* short-acting β_2-agonist, *SABINA* SABA use IN Asthma, *UMIC* upper-middle-income country, *USD* United States dollar

Per capita SABA use was higher than per capita controller use in 23 of the 28 countries analysed (Table 2). Per capita SABA use ranged from 3983 doses/10,000 persons/year (China) to 1,157,741 doses/10,000 persons/year (Australia), and per capita controller use ranged from 1434 doses/10,000 persons/year (Central America) to 313,105 doses/10,000 persons/year (New Zealand [NZ]; Fig. 2, Table 2). Among regions, per capita SABA and controller medication uses were the highest in the Middle East (165,077 and 96,507 doses/10,000 persons/year, respectively), with the largest quantity of SABA and controller medication use observed in Saudi Arabia (181,026 doses/10,000 persons/year) and Turkey (126,266 doses/10,000 persons/year), respectively (Table 2; Supplementary Materials Fig. S2). HICs had the highest per capita SABA and controller medication use (169,692 and 84,455 doses/10,000 persons/year, respectively), with the majority of SABA and controller medication use observed in Australia and NZ, respectively (Table 2; Supplementary Materials Fig. S3).

Greenhouse Gas Emissions Associated with Short-Acting β_2-Agonist and Controller Medication Use

GHG emissions from SABA and controller medication use across all countries were

approximately 2.7 and 1.2 million tonnes CO_2e, respectively, with SABA accounting for 70% of total inhaler-related GHG emissions. SABA-related GHG emissions as a proportion of total inhaler-related GHG emissions ranged from 29% (Japan) to 93% (Colombia) and comprised > 50% of total inhaler-related GHG emissions in 24 of the 28 countries analysed (Fig. 1, Table 2). As a proportion of total inhaler-related GHG emissions, SABA-related GHG emissions were the highest in the Middle East (81%) and were higher among UMICs (77%) than among HICs (72%) and LMICs (54%; Table 2).

Per capita SABA-related GHG emissions were higher than per capita controller medication-related GHG emissions in 24 of the 28 countries analysed. Per capita SABA-related GHG emissions ranged from 0.5 tonnes CO_2e/10,000 persons/year (China) to 153.7 tonnes CO_2e/10,000 persons/year (Australia), while per capita controller medication-related GHG emissions ranged from 0.2 tonnes CO_2e/10,000 persons/year (China and Central America) to 36.7 tonnes CO_2e/10,000 persons/year (NZ; Fig. 2, Table 2). Among regions, per capita SABA-related GHG emissions were the highest in the Middle East (22 tonnes CO_2e/10,000 persons/year) and lowest in Asia Pacific (4 tonnes CO_2e/10,000 persons/year), with the most per capita GHG emissions in the Middle East contributed by Saudi Arabia (24.3 tonnes CO_2e/10,000 persons/year; Table 2; Supplementary Materials Fig. S2). Overall, per capita SABA-related GHG emissions were higher among HICs than among UMICs and LMICs (22, 6 and 4 tonnes CO_2e/10,000 persons/year, respectively), with the most per capita GHG emissions among HICs ascribed to Australia (Table 2; Supplementary Materials Fig. S3).

The GHG emission estimates associated with pMDIs and DPIs for each country are listed in Supplementary Materials Tables S2 and S3, respectively.

Analyses Performed Using SABA use IN Asthma III Data

Short-Acting β_2-Agonist Overuse and Associated Greenhouse Gas Emissions

Across countries, > 90% of SABA prescriptions were given to patients overusing SABA (Fig. 3). In these patients, the proportion of SABA prescriptions given was similar across all treatment steps and ranged from 88% and 87% (Asia Pacific) to 95% and 94% (Africa) in those with and without SABA OTC, respectively. Among national economies, the proportion of SABA prescriptions given ranged from 90% and 89% (LMICs) to 95% and 95% (HICs) in patients with and without SABA OTC, respectively.

Per capita SABA overuse-related GHG emissions with and without SABA OTC, respectively, were 1106 and 937 tonnes CO_2e/10,000 persons/year in patients at GINA steps 1–2 versus 793 and 669 tonnes CO_2e/10,000 persons/year in those at GINA steps 3–5 (Fig. 3). Across regions, per capita SABA overuse-related GHG emissions with and without SABA OTC ranged from 586 and 508 tonnes CO_2e/10,000 persons/year (Asia Pacific) to 1204 and 987 tonnes CO_2e/10,000 persons/year (Africa and Latin America), respectively. Among national economies, per capita SABA overuse-related GHG emissions with and without SABA OTC ranged from 642 and 468 tonnes CO_2e/10,000 persons/year (LMICs) to 958 and 865 tonnes CO_2e/10,000 persons/year (HICs), respectively (Fig. 3). The difference in per capita SABA overuse-related GHG emissions, with and without SABA OTC, was the most pronounced in Africa (22.6% decrease) compared with that in other regions (Middle East, 12.2% decrease; Asia Pacific, 13.3% decrease; Latin America, 11.3% decrease) and among LMICs (27.1% decrease) versus UMICs (14.2% decrease) and HICs (9.7% decrease).

The number of SABA prescriptions given to patients overusing SABA with and without SABA OTC and associated GHG emissions are provided in Supplementary Materials Table S4.

DISCUSSION

Our findings, based on inhaler sales data, indicate high SABA use among patients with respiratory diseases, accounting for > 50% of total inhaler use and inhaler-related GHG emissions in most countries assessed. Per capita SABA use and associated GHG emissions were the greatest in Australia, in the Middle East and among HICs. Moreover, an analysis of SABINA III data revealed that SABA overuse (≥ 3 canisters/year) drove most SABA prescribing in asthma (> 90%). Per capita SABA overuse-related GHG emissions with and without SABA OTC were more pronounced in Africa and Latin America, respectively, and among HICs. Furthermore, the impact of SABA OTC purchase on per capita GHG emissions was greater among LMICs than among UMICs and HICs. Overall, regardless of the economic status of the countries studied, SABAs were the most commonly used inhalers, indicating suboptimal management of respiratory conditions [32], and contributed substantially to the carbon footprint of inhaler treatment. Therefore, efforts to optimise the management of respiratory diseases to curtail high SABA use could improve patient outcomes and result in substantial carbon savings in the healthcare sector.

Our results align with those of the SABA CARBON-Europe and Canada study, where SABA use generated 66% of total inhaler-related GHG emissions [33]. Moreover, the present study extended these findings worldwide to include geographical regions not commonly explored. Overall, the Middle East produced the highest per capita SABA use and related GHG emissions across all respiratory indications, chiefly contributed by Saudi Arabia. This aligns with previous reports from the Middle East documenting poor asthma control and non-adherence to prescribed ICS medication in most patients investigated [34, 35]. Indeed, suboptimal disease control has been reported in Turkey [36] and Saudi Arabia [37], with the Turkish study citing inadequate patient understanding of the role of ICS in attaining asthma control [36].

The greatest per capita SABA use and associated GHG emissions were from HICs; the highest emissions were observed from Australia and NZ, where despite an epidemic of asthma-related deaths (including children aged 5–-17 years) in both countries during the 1960s and 1980s, which was attributed to inappropriate use of β-agonists [38–40], SABAs continue to be widely prescribed [41–43]. Although SABAs are not available for OTC purchase in NZ [44], with national dispensing data documenting a progressive decrease in SABA use following publication of National Asthma Guidelines in 2020 [45], a national report revealed that 47% of patients with asthma who were dispensed an ICS and SABA were given more SABA than ICS [43]. The high per capita reliever use in Australia may be explained by government regulations permitting dispensing of up to 1 months' supply of prescribed SABAs and OTC sale of one canister per purchase to patients with asthma, with automatic repeat prescriptions via electronic medical records valid for up to 12 months [46, 47]. Interestingly, although both Australia and NZ report a similarly high asthma prevalence (10.7% and 11.4% in 2020–2021, respectively), with both countries having universal public health systems and subsidised access to ICS-containing therapies [48–50], a higher per capita SABA use and lower per capita controller use were reported in Australia than in NZ. This finding is likely attributable to better self-reported adherence to ICS-containing therapies in NZ, possibly enhanced by lower patient co-payments and availability of SABA OTC in Australia since 1983 to reduce delays in accessing reliever inhalers for patients with acute symptoms [41, 48, 51]. In November 2016 in Melbourne, Australia, the convergence of environmental and patient factors triggered a thunderstorm asthma epidemic of unprecedented severity that resulted in several thousand acute respiratory presentations to emergency departments and ten deaths, for which health services, emergency services and the community were not prepared [52–54]. Given the need to ensure optimal management of any future epidemic thunderstorm asthma events and the need to protect at-risk asthma populations [51], it is unlikely that purchase of

SABA OTC in Australia will be subject to regulation, despite results from an Australian community pharmacy-based survey classifying 70.1% of participants who purchased SABA OTC from community pharmacies as over-users (reporting SABA use more than twice weekly during the 4 weeks before the study) [41]. Such patients were more likely to experience uncontrolled asthma and require oral corticosteroids (OCS) to manage poor symptom control and exacerbations than those who did not overuse SABA [41]. These findings raise concern, as even intermittent OCS use (3–7 days) is associated with greater odds of adverse outcomes once a lifetime cumulative OCS exposure of 1000 mg is exceeded [55–57].

Analyses of the SABINA III study [18] revealed that most SABA prescriptions (> 90%) were given to patients overusing SABA, a finding comparable with that observed in the SABA CARBON-Europe and Canada study, where the proportion of SABA prescriptions given to patients overusing SABA ranged from 69% (Italy and Sweden) to 94% (Canada [Nova Scotia]) [33]. Such findings suggest improper prescription practices globally, underscoring the need for healthcare providers (HCPs) to evaluate the volume and frequency of SABA use in patients during routine reviews to assess risk before prescribing additional SABA. Overall, the percent difference between per capita SABA overuse-related GHG emissions with and without SABA OTC purchase was higher among LMICs than among UMICs and HICs. Thus, unregulated OTC availability of SABA in LMICs [58] might further provoke SABA overuse and expand the carbon footprint of asthma treatment in these countries. Notably, although the Asia-Pacific region had the lowest per capita SABA overuse-related GHG emissions with and without SABA OTC, this may not be indicative of good disease control or optimised treatment, as patients prefer oral therapies over inhaled medication in these countries [59].

The clinical implications of this study are wide ranging and provide an understanding of how, based on inhaler sales data, high SABA use drives the carbon footprint associated with respiratory treatment. Overall, the real-world variations in total inhaler-related GHG emissions observed across countries may be explained by differing healthcare policies, the non-availability of ICS-containing controller medications in many LICs, medications costs, healthcare insurance coverage [60, 61] and sociocultural contexts, all of which may have influenced HCP and patient preferences for inhaler use. Our findings from the SABINA III study indicate that SABA over-reliance is highly prevalent among both patients and HCPs. Since 2019, GINA has not recommended as-needed SABA monotherapy, based on evidence of increased morbidity and mortality [62]. Consequently, it is essential to implement the latest evidence-based treatment recommendations in clinical practice while fostering a strong partnership between HCPs and patients through shared treatment decision-making to improve clinical outcomes. This may also involve regulation of prescribing, dispensing and OTC sales of SABA, in parallel with improved access to ICS-containing medication, healthcare and affordable alternatives to SABA relievers, especially in countries with fragmented healthcare systems. Furthermore, factors that contribute to suboptimal disease control and drive increased demand for HCRU, such as incorrect inhaler technique, inappropriate medication use and poor treatment adherence [63], must be addressed to improve clinical outcomes and contain GHG emissions from the healthcare sector. This, coupled with asthma awareness campaigns, health promotion programmes and continuing medical education to facilitate adoption and application of treatment recommendations among HCPs [64], should help reduce the inequities that exist within healthcare systems, especially in LMICs, and reduce their respective healthcare sector-related emissions.

Several limitations of this study should be acknowledged. This study does not provide a complete quantification of the carbon footprint of inhalers to respiratory care within a single dataset; however, two distinct data sources were used, IQVIA MIDAS and SABINA III, to determine total inhaler use across all respiratory indications and SABA overuse in asthma, respectively. Most patients from SABINA III were recruited from specialist care and were

therefore classified as having moderate-to-severe asthma [18]; thus, the study population may not be truly representative of the overall asthma patient population or reflect the way asthma is currently being managed across countries and regions. Nonetheless, data from the SABINA III study provided valuable insights on the carbon footprint of asthma medications, especially SABA prescriptions by practicing physicians, across a broad range of LMICs, UMICs and HICs on a global scale. Inhaler sales and prescription/dispensing data may not reflect actual medication use or treatment adherence and do not consider medication stockpiling; therefore, GHG emissions may have been overestimated. Inhaler-related CO_2e emissions were derived from published guidelines and studies and pharmaceutical LCAs and, therefore, are subject to variability over time. However, these uncertainties were overcome, at least in part, by performing a sensitivity analysis that considered updated guidelines, product LCAs and recently published studies [23–28] and reported relatively small increases of up to approximately 8% in inhaler-related GHG estimates. Data on the use of other SABA formulations and inhaled reliever medication other than SABAs and their associated emissions were not assessed in this study. Lastly, the small sample size of the regional analyses in SABINA III poses a challenge in identifying the principal country-by-country GHG contributors, as they do not afford further stratification to that level. However, despite these limitations, the global IQVIA sales data reflect most channels through which inhaled medications may be accessed. In addition, a standardised methodology was applied to quantify the carbon footprint of inhaled medications and to prevent confounding from differences in dose and actuation counts across inhalers, and data from > 8000 patients from SABINA III [18] enabled an assessment of the global environmental impact of SABA overuse.

CONCLUSIONS

In conclusion, this retrospective cohort study is the first to quantify inhaled medication use and associated GHG emissions across Africa, Asia Pacific, Latin America and the Middle East. Overall, across all respiratory indications, SABAs accounted for > 50% of total inhaler use and inhaler-related GHG emissions in most countries analysed. Moreover, > 90% of SABA prescriptions for asthma were given to patients overusing SABA, highlighting a definable population to target. These findings suggest that implementing international recommendations that reduce high SABA use in respiratory care, especially in asthma, and adopting patient-centric principles of improving disease management would optimise patient outcomes while enabling healthcare systems to meet their carbon reduction targets.

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Data Availability. Data underlying the SABINA III findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for clinical research studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for clinical research studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Declarations

Conflict of Interest. Ashraf Alzaabi and Hao-Chien Wang have no conflicts to declare. John P Bell, Nigel Budgen, Hisham Farouk and Ekaterina Maslova are employees of AstraZeneca and own stock in AstraZeneca. Felicia Montero-Arias has been a part of clinical studies sponsored by AstraZeneca, Novartis, NIH and Moderna; has received advisory board fees from AstraZeneca, Novartis and Roche; and has received payment for speaking engagements from AstraZeneca, Novartis and GlaxoSmithKline. David B. Price has a board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme and Thermo Fisher; has consultancy agreements with Airway Vista Secretariat, AstraZeneca, Boehringer Ingelheim, Chiesi, EPG Communication Holdings Ltd, FIECON Ltd, Fieldwork International, GlaxoSmithKline, Mylan, Mundipharma, Novartis, OM Pharma SA, PeerVoice, Phadia AB, Spirosure Inc., Strategic North Limited, Synapse Research Management Partners S.L., Talos Health Solutions, Theravance and WebMD Global LLC; has received grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Boehringer Ingelheim, Chiesi, Mylan, Novartis, Regeneron Pharmaceuticals, Respiratory Effectiveness Group, Sanofi Genzyme, Theravance and UK National Health Service; has received payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Mylan, Mundipharma, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme; has received payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Mundipharma, Mylan, Novartis and Thermo Fisher; has stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); has a 5% shareholding in Timestamp, which develops an adherence monitoring technology; is a peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and was an expert witness for GlaxoSmithKline. David J. Jackson has received advisory board and speaker fees from AstraZeneca, GlaxoSmithKline, Sanofi, Boehringer Ingelheim and Chiesi and research grants from AstraZeneca.

Ethical Approval. This study was conducted in compliance with the Declaration of Helsinki.

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