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Title

Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data.

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Abstract

Objectives

Dry powder inhalers (DPIs) have a substantially lower global warming potential than pressurized metered-dose inhalers (MDIs). To help mitigate climate change, we assessed the potential reduction in CO2-equivalents when replacing MDIs by DPIs in the Netherlands, and estimated the associated cost.

Design

We performed a four-step analysis based on data from two national databases of two independent governmental bodies (Dutch National Healthcare Institute and the Dutch Healthcare Authority). First, we calculated the number of patients with Chronic Obstructive Pulmonary Disease (COPD) and asthma that were using inhalation medication (2019). Second, we calculated the number and total of daily defined doses of MDIs, DPIs, and soft mist inhalers and the number of spacers per patients, dispensed by non-hospital based pharmacies in 2019. Third, we estimated the potential reduction in CO2-equivalents (eq.) if all eligible patients (≥7 years old; COPD with ≤1 exacerbation per year) would switch from using MDIs to using DPIs as eco-friendly alternatives. Fourth, we performed a cost-effectiveness analysis.

Results

In 2019, 1.4 million patients used inhalers for COPD or asthma treatment. A total of 322 million defined daily doses (DDDs) from inhalers were dispensed, of which – after the exclusion of nebulisers – 49.1% were from MDIs**.** We estimated that this use could be reduced by 69% leading to annual reduction in emissions of 52-58 million kg CO2eq. and saving € 25.7 million annually.

Conclusions

In the Netherlands, substitution of MDIs to DPIs for eligible patients is theoretically safe and in accordance with medical guidelines, while reducing emissions by 55 million kg.CO2eq. on average and saving over €25 million per year. This study confirms the potential climate and economic benefit of delivering eco-friendlier respiratory care.

Strengths and limitations of this study

- Given availability and reliability of the data, the present analysis can easily be replicated elsewhere which allows for international comparison and aggregation.
- Implementation challenges remain underexposed.

INTRODUCTION

Climate change is the greatest global health threat of this century, inflicting a range of ill health outcomes including (re-)emerging zoonoses such as Covid-19, non-communicable diseases and mental health disorders.[1, 2] Paradoxically, the health care industry contributes substantially to global warming. If global health care were a country, it would rank fifth for greenhouse gas emissions and its environmental footprint is substantial.[3, 4] In the Netherlands, the healthcare sector is responsible for 6-7% of the total national CO_2-eq. emission.[5] Hence, the Dutch healthcare sector could play a significant role in meeting the national climate policy goals, thereby preserving planetary health and population health that depends on it.

Among the impactful solutions to deliver more sustainable healthcare is the choice of inhaler type to deliver medication to the lungs of patients with asthma, allergies, or chronic obstructive pulmonary disease (COPD). Pressurized metered-dose inhalers (MDIs) contain propellants known as hydrofluorocarbons (HFCs), potent F-gases that account for 15 megaton CO_2-eq. (0.03%) of all greenhouse gas emissions worldwide (RIVM, 2021). HFCs will be phased out by two-thirds by 2030 in the European Union by cutting sale and use in equipment like air conditioning and refrigeration. However, their application in metered dose inhalers is exempted from this regulation.[6] MDIs contain either the propellant HFC-134a or HFC-227ea. Another commonly used class of inhalers are dry-powder inhalers (DPIs). These are as safe and effective in most patients but do not contain greenhouse gases which is why their life cycle assessments are substantially lower than those of MDIs.[7]

BOX 1. GLOBAL WARMING POTENTIAL (GWP)

The global warming potential is the heat absorbed by any greenhouse gas in the atmosphere compared to the mass of CO_2. The GWP of CO_2 is 1.0. The GWPs of HFC-134a and HFC-227ea, hydrofluorocarbons used in metered dose inhalers, are 1,330 and 3,220.

Several studies have assessed the costs and benefits of switching to medication with a lower global warming potential (see Box 1). Wilkinson et al. found considerable reductions in both CO_2 emissions and pharmaceutical costs.[8] Janson et al. recommend that "the lower carbon footprint of DPIs should be considered alongside other factors when choosing inhaler devices."[9] In their review, Starup-Hansen et al. recommend to update guidelines: "guidance should consider the potential benefits of advising DPIs as the device of choice in new diagnoses of asthma and COPD as well as the benefits of switching patients currently using MDIs to DPIs where clinically appropriate."[10] These recommendations have been recently adopted in the

guidelines 'Asthma in adults'[11] and 'COPD'[12] of the Dutch College of General Practitioners. Among other updates, these guidelines contain the same modest, though historical, reference to considering the environmental impact of the medicine of choice for the prescribing physician (see Box 2).

BOX 2. NHG-GUIDELINES 'ASTHMA IN ADULTS' (2020) AND 'COPD' (2021)

One of the criteria in de decision aide for choosing an inhaler device

"A general objection against metered dose inhalers is that they contain a greenhouse gas with a strong environmental impact."

Note

"Metered dose inhalers use HFC propellants. The F-gas hydrofluorcarbon does not affect the ozon layer but is a strong greenhouse gas. The environmental impact of 1 inhalation is 25 times larger than a dry-powder inhalation. Environmental impact of production, transport and waste processing (..) have not been included."

To understand the implications of changing from MDI to DPI-use for policy, practice, and patients in another setting, we build on the cost and carbon analysis of Wilkinson et al.[8]. In this paper, we calculated the environmental impact of changing use of MDIs to more eco-friendly DPIs in Dutch primary and secondary respiratory healthcare and analysed the associated pharmaceutical costs.

METHODS

We performed a four-step data analysis of prescription data in order to estimate the carbon equivalent footprint of prescribed inhalers over a one-year period (2019). We determined how much inhalation medication could be attributed to the following patient groups: 1) asthma, 2) COPD, 3) severe COPD and 4) children younger than 7 years of age. Estimations were based on the GIP database (Genees- en hulpmiddelen Informatie Project | Medicines and medical devices Information Project) of the Dutch National Health Care Institute and the DIS database (DBC Informatie Systeem | Diagnosis-Treatment Combination Information system) of the Dutch Healthcare Authority, both independent government bodies residing under the Dutch Ministry of Health, Welfare and Sports. GIP is an independent and representative information system containing data on the use and cost of prescription drugs and medical devices.[13] DIS contains information of all treatment trajectories in Dutch medical specialist care, including pulmonary medicine, mental health care, forensic care and rehabilitation.[14] Health care providers are legally required to deliver these data for policy making and regulation. A

Supplementary File contains the complete data analysis protocol and additional information regarding methodological details, assumptions and choices made.

First, we calculated the number of patients with asthma or COPD that used inhalation medication in the Netherlands in 2019 by joining diagnoses codes to inhalation medication. Second, we calculated the number of defined daily doses (DDDs) discriminating between MDIs and DPIs. Nebulisers were excluded from the analysis since they do not contain propellants and due to their size and dependency on electricity, they are not to be considered an alternative to MDIs for use by patients at home. Third, we determined the volume of MDIs that could hypothetically be replaced by DPIs in a safe and medically responsible way. We estimated the size of this volume in DDDs, according to current medical guidelines excluding children younger than 7 years of age and those patients with severe COPD having at least two exacerbations per year. In our data the subgroups 'younger than 7 years' and 'severe COPD' consume 16.3% of the total medication delivered by MDI. So, if we would disregard their MDI-use, and only replace inhalers of the remaining patients, we could achieve a 83.7% reduction of MDI-use. In these two subgroups (younger than 7, severe COPD), it is possible to safely replace MDIs in inhalation corticosteroid (ICS) maintenance therapy for DPIs, without any negative medical impact. Here, breathing is not hampered during maintenance therapy and an immediate effect of ICS is not required. We nonetheless chose a more conservative estimate of change. We used the frequently stated figure of 10% MDI-use in Sweden as a proxy assuming Sweden and The Netherlands are comparable in terms of a variety of social-epidemiological indicators.[15, 16] Hence it is likely that the latter country could approach Sweden's level of DPI-prescription to an again more conservative, putative 15%. From the current level of 49.1% down to 15% MDI-use equals a 69% reduction, which is less than the previous 83.7%. Based on our data we know how many canisters of each type were prescribed in 2019 applying two conversion tables, one published by Wilkinson et al.[8] and the other one by Jeswani & Azapagic.[7] Since they use different resources for quantification we have used a range instead of an average. Finally we calculated the kg CO2-eq. decrease as a consequence of this 69% reduction in MDI-use. In the fourth and last step we calculated if this potential replacement could be achieved in a cost-neutral way. By determining both the current costs of medication, spacers and estimated replacement costs we calculated the difference. For the replacement costs we applied two realistic scenarios, one is the low cost scenario in which MDIs are replaced by low cost DPIs. In the second scenario MDIs are replaced by average-cost DPIs. People living with COPD or asthma were not involved in the design and conduct of this study.

RESULTS

In 2019, 1,409,497 patients used inhalation medication in the Netherlands, and they were delivered a total of 322,269,871 defined daily doses (Table 1). In addition 583,704 spacers were administered to 548,482 (MDI-using) patients meaning that 67% of 819,417 MDI-using patients could use their inhaler together with a yearly to-be-replaced spacer, as recommended by Dutch medical guidelines.

Table 1. Inhalation medication in the Netherlands 2019

Inhaler type	*Number of patients **	*Number of DDDs ***	*% of total DDD use*
Metered-dose (MDI)	819,417	155,794,499	49.1%
Dry powder (DPI)	833,383	161,589,119	50.9%
Nebulisers (excluded in further analysis)	30,597	4,886,253	
MDI and/or DPI (included)	1,403,270	317,383,617	100%
MDI and/or DPI and/or nebulisers (total group)	1,409,497	322,269,871	

** Users may use different types of inhalers at the same time*

*** Defined daily dose*

After excluding the use of nebulisers, we focused on the group of 1,403,270 patients using MDI and/or DPI, who were prescribed over 317,383,617 DDDs in 2019 (Table 1).

The total amount of medication delivered in 2019 by MDI is 155,794,499 DDDs. We observed that 49.1% of the medication has been delivered using MDIs, 50.9% per DPIs (Table 1).

Not all inhalation medication can be delivered by both types of inhalers, e.g. short-acting beta agonists (SABA) and short-acting muscarinic-antagonists (SAMA).

The number of patients that could hypothetically switch safely to DPIs with the same content would be using 151,032,788 DDDs, equal to 4,453,183 canisters.

Using the Wilkinson's conversion table with "mg HFC per canister", delivers a reduction of 58 million kg CO2.eq.[8] Using the conversion table from Jeswani & Azapagic provides a reduction of 52 million kg CO2.eq.[7] The range being 51,782,897 – 57,581,368 million kg CO2.eq. with an average of 54,682,133 kg.CO2eq. corresponding to 41,554 kg HFC; HFC-134a for the better part (Figure 1).

We calculated if shifting to DPIs could be achieved in a cost-neutral way. We determined both the current costs of medication and spacers, we estimated replacement costs and we calculated the difference. For the replacement costs we applied two realistic scenarios, one is a low cost scenario in which MDIs are replaced by low cost DPIs. In the second scenario MDIs are replaced by average cost DPIs in current market share (Table 2).

Table 2. DDD Volumes, costs of medication and spacers

	MDI-use in 2019, in medication groups: SABA, LABA, ICS, SAMA, LABA-ICS, LABA-SAMA-ICS*	69% of MDI-use (part that can theoretically be safely replaced)	Replacement of MDI by low cost DPI	Replacement by DPI, in current market share
Volume in DDD	151,032,789	104,212,624	104,212,624	104,212,624
Medication costs	€ 89,574,691	€ 61,806,537	€ 48,486,061	€ 72,801,318
Costs of spacers	€ 17,882,319	€ 12,338,800	n.a.	n.a.
Total costs	€ 107,457,010	€ 74,145,337	€ 48,486,061	€ 72,801,318

*
SABA = short-acting beta agonists | SAMA = short-acting muscarinic-antagonists
LABA = long-acting muscarinic-antagonists |LAMA = long-acting muscarinic antagonists
ICS = inhalation corticosteroids

If the percentage of DDD's from MDI could be reduced from 49% to 15% this 69% reduction implies a decrease of 104,212,624 DDDs which equals EUR 74,145,337 (medication + inhalers cost EUR 61,806,537 plus the cost of spacers EUR 12,338,800). Replacing this by low cost DPIs, would incur a cost of EUR 48,486,061, saving approximately EUR 25.7 million annually.

DISCUSSION

The healthcare sector needs to decrease greenhouse gas emissions to help mitigate climate change. This may be viewed as a moral and practical obligation in times of climate crisis and the global health emergency it implies.[17] To achieve this, substantiated and medically safe eco-friendly alternatives are necessary. In this study, we assessed the hypothetical impact of converting eligible patients from using MDIs to using DPIs in the Netherlands, both in terms of greenhouse gas emissions and in cost. With these outcomes we seek to offer insight into the impact of making this change and to inspire health care professionals to act climate responsibly which is congruent with announcements of professional organisations such as the British Thoracic Society,[18] the European Respiratory Society,[19] the International Society for Quality in Health Care,[20] and the US National Academy of Sciences, Engineering, and Medicine.[21]

Our results show that a sizeable reduction in greenhouse gas emissions is attainable in the Netherlands with a readily available eco-friendly alternative. The financial impact of this shift depends on the choice for either a low-cost option or a more expensive option, but we demonstrated a cost reduction is feasible if done right. The estimated cost-saving does not include financial calculations of patient training or potential drawbacks of substitution such as lower adherence leading to increased GP visits or hospital admissions.

These results are in accordance with earlier studies [8, 9, 22] but we were relatively stringent in our eligibility criteria (which patients are able to change safely), and more selective as to what brands to include for the financial impact estimation. Obviously the outcomes refer to Dutch respiratory health care, its specific patient population and medication use.

In estimating the environmental impact of MDIs, we considered their full amount of propellants. We did not subtract unknown quantities of propellants that may remain in the canister after use, as we assumed that sooner or later 100% of these gases will be released into the atmosphere. We did not include other environmental impacts of MDIs nor DPIs, as would be done in a full life cycle assessment (LCA). LCAs typically include the whole spectrum of production, packaging, distribution, distribution, usage, waste, etc. However, MDIs' global warming effect is mainly caused by their use (95-98%), not by the manufacturing of this class of inhalers.[7, 8] Though DPIs as opposed to pressurized MDIs generate much lower GWP, LCAs imply other harmful impacts that eventually should be included in a comparison such as human toxicity, marine eutrophication or fossil depletion.[7]

Our study implies that if medically safe and possible, choosing the medicine or device with the least environmental impact is imperative in times of global climate crisis. This is not just about patients' choice, as may be suggested by NICE's patient decision aid.[23] It could be considered

the prescriber's task as well. Therefore it should be integrated in medical guidelines and standards as part of health care quality improvement trajectories much like Mortimer et al. have elegantly proposed and practiced.[24] This should not affect the established fact that suitable patient training and monitoring of inhalation techniques are a sine qua non for effective inhaler use for all a patients, especially for children.[25, 26] In the Netherlands, general practitioners recently updated their guidelines on the management of asthma and COPD, and included a recommendation to consider the environmental impact of the medicine of choice (see Textbox 2). In view of the health emergency represented by the climate crisis we recommend that pulmonologists also consider to update national and local guidelines and appreciate the potential benefits of advising green inhalers as the device of choice in new diagnostics of asthma and COPD and the benefits of resetting patients currently using MDIs to DPIs if safe and possible. In 2019 Belgian pulmonologists recommended the use of DPIs to lung patients not just because they can deliver better treatment results for asthma and COPD but also because they are "far less damaging to the environment than traditional propellant driven aerosols."[27]

Evidently, the chosen medication should be fitting for the individual patient. It is beyond the scope of this study to include all specific circumstances in which patients cannot use DPIs. Since daily use and emergency use are quite different, there have been reservations about DPIs in case of exacerbations especially since both the expiratory flow and the inspiratory ('trapped air') flow of breath are obstructed leading to patients' preference for MDIs in such circumstances. In Sweden soft mist inhalers are recently used more often in such cases because they require minimal inspiratory power. Wilkinson et al. referring to a data analysis of the NHS Business Services Authority, suggest that in England "clinicians believe the vast majority of patients can use a DPI effectively."[8]

Apart from climate and economic benefits we identified more advantages of replacing MDIs with DPIs as suggested by research and practice (Table 3).

Table 3. Plausible advantages of replacing MDIs with DPIs.

Plausible advantages	References (if present)
Less critical errors are made using DPIs as compared to MDIs.	Chrystyn H, van der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, Thomas M. Device errors in asthma and COPD: systematic literature review and meta-analysis. NPJ Prim Care Respir Med. 2017 Apr 3;27(1):22.
Sometimes MDIs are used when empty, which may lead to poor disease control and less quality of life.	Conner JB, Buck PO. Improving asthma management: the case for mandatory inclusion of dose counters on all rescue bronchodilators. J Asthma. 2013 Aug;50(6):658-63. doi: 10.3109/02770903.2013.789056. Epub 2013 Apr 29. Tsangarides A, Wilkinson A, Mir F. Disadvantages of salbutamol pressurised metered-dose inhalers (pMDIs). *Thorax* 2018;73:A193-A194.
Some MDIs are unknowingly considered empty and are disposed of leading to unnecessary costs.	Holt S, Holt A, Weatherall M, Masoli M, Beasley R. Metered dose inhalers: a need for dose counters. Respirology (Carlton, Vic.). 2005 Jan;10(1):105-106.
Following Dutch clinical guidelines, MDI-users should yearly receive a new spacer. During 2019 however, only 67% of MDI-using patients received it which implies suboptimal quality of care.	
Changing to DPI may improve guideline adherence because use of a spacer is not required for DPI.	
Use of DPI requires no spacers and consequently does at least not generate nonreusable plastics	

The present study does not discuss implementation questions, or probable (dis-)advantages of both MDIs and DPIs. It is certainly useful to address the preferences and prejudices of patients and professionals and we know citizens, patients and professionals are increasingly willing to choose eco-friendly alternatives but there is no knowledge on this specific shift from MDIs to

DPIs.[28-30] Next to that, while some practical (dis-)advantages of both MDIs and DPIs are known we recommend explaining these to patients similar to the NICE decision aid as well as to professionals.[23, 31] For example, most MDIs do not have dose-counters. While all DPIs have a counter they do not necessarily prevent using an empty device. Without a dose-counter it may be hard to know how many doses are left in the device. Unknowingly using empty MDIs could lead to avoidable exacerbations or even avoidable hospital admissions. Unknowingly replacing MDIs that still contain medication would incur unnecessary cost.[32] Adherence to inhalation instructions may be an issue when it comes to changing, but this is already an issue e.g., not every patient with an MDI uses the recommended, though bulky, spacer. Also, adherence to inhalation medication therapy should be promoted by repeated inhalation instruction.[33] Switching without sufficient instruction may result in uncontrolled, exacerbations and increased use of health care services. Uniformity of the devices in case of multiple inhaler use is relevant here. Such questions pertain to responsible implementation, a subject we will address in our follow-up study in the context of Covid-19 recovery plans.

The pharmaceutical industry meanwhile continues to develop and study inhalers with lower climate impacts. And new propellants will enter the market. For patients who are dependent on MDIs, this is meaningful. Given that these developments have not yet entered the market and knowledge of these is still limited, we will not elaborate on this matter. Research should nonetheless include more green metrics into their output and outcome parameters. This would enable meta-analyses and evidence-based climate-responsible innovation in health care.

CONCLUSIONS

Large scale replacement of MPIs with DPIs would have a substantial climate impact in respiratory healthcare. In 2019 about 1.4 million patients using MDI and/or DPI, were prescribed over 317 million DDDs. The use of MDIs is more or less equally prevalent among patients with COPD and patients with asthma. So almost half (49%) of the medication has been delivered using MDIs that have a relatively high global warming potential. The percentage of DPI-delivered inhalation medication that can safely be replaced is estimated to be 69%, resulting in an environmental health benefit of 54,682,133 kg.CO_2 eq. on average, which equals the carbon dioxide emission of just over 2700 Dutch households. This shift could be achieved in a cost-neutral way. In fact it may lead to a cost reduction of approximately EUR 25.7 million per year in Dutch respiratory health care.

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Contributors

All authors meet the required criteria for authorship. PtH contributed to the conception, designed the study, did most of the analysis and interpretation of the data. PvH, IW, JK, PdH, NC, EB, PH helped analyse and interpret the data for health care practice and implementation issues, and revised the manuscript. HCO contributed to the conception, drafted the manuscript and revised it for intellectual content.

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Supplementary File

Data analysis protocol (Appendix)

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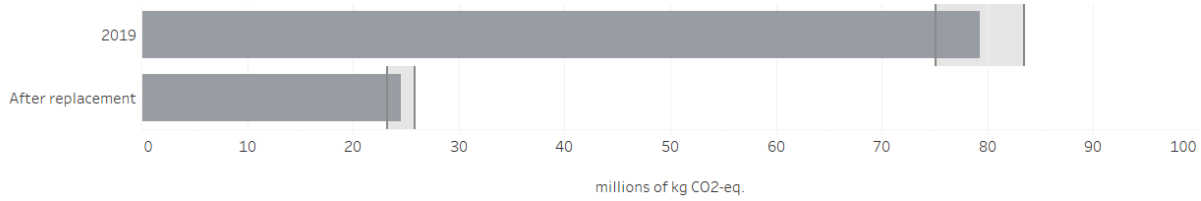
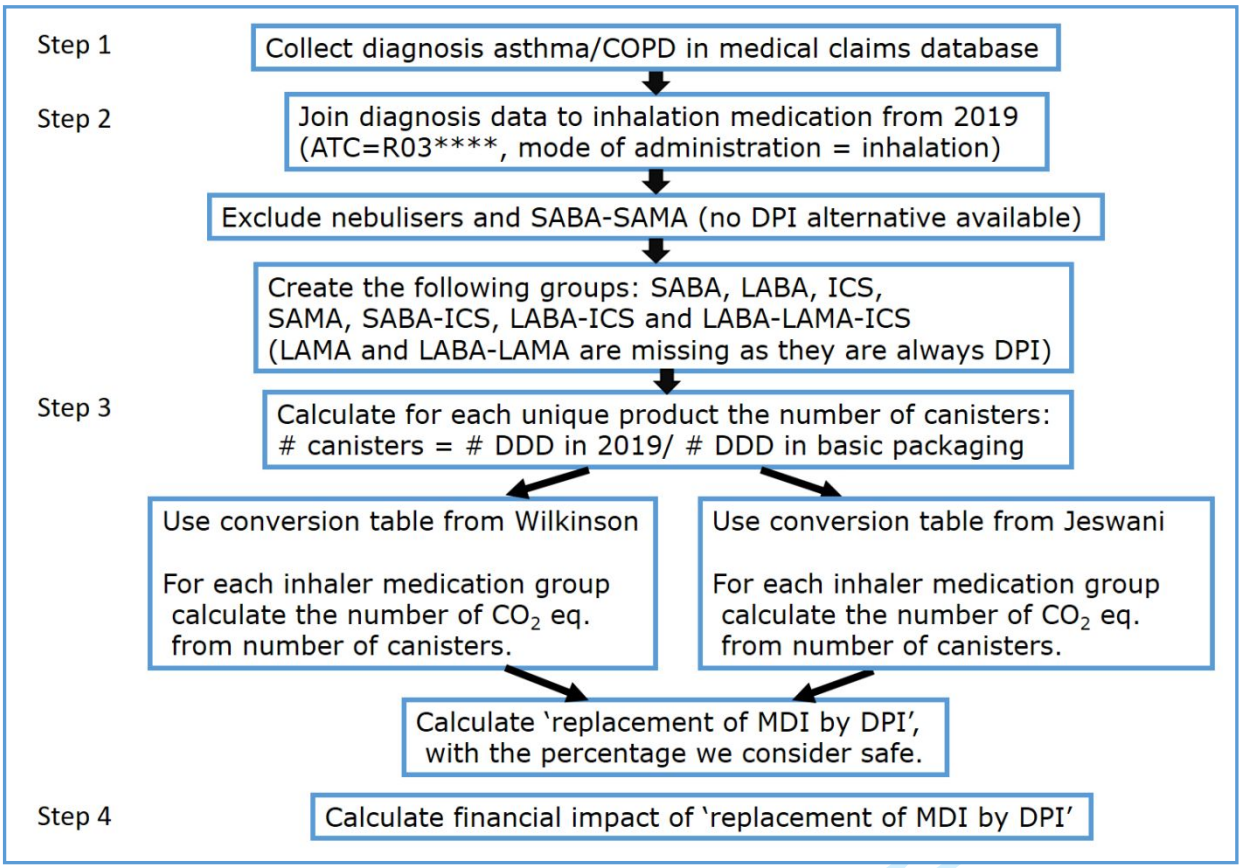
Fig. 1 Environmental impact (in $kgCO_2$ equivalents) of a hypothetical replacement of MDIs in The Netherlands.



Introduction

The most important steps of our method to calculate the impact of replacing MDIs by DPIs on greenhouse gas emissions in Dutch healthcare, are shown in Figure 1.

Figure 1. Steps to calculate the impact of conversion of MDI to DPI



Our data-analysis protocol is:

Step 1: Collect diagnoses asthma/COPD from medical claims database

Use the DIS database (DBC Informatie Systeem | Diagnosis-Treatment Combination Information system) to collect the identifiers and diagnoses of patients that received care for asthma or COPD between 2012 and 2019. The DIS database is a medical claims database covering all medical care giving to all Dutch citizens. Private care included as well. The independent government body Dutch Health Care Authority (Nederlandse Zorgautoriteit) owns this database.

The reason for this initial step is to find out how many MDI DDDs were prescribed for patients with severe COPD, as guidelines do not consider them eligible for DPI. Also, we wanted to know how MDIs are distributed between asthma and COPD.

Step 2: Join these diagnoses to the inhalation medication given in 2019

The GIP database (Genees- en hulpmiddelen Informatie Project | Medicines and medical devices Information Project) contains all prescriptions of all Dutch citizens from pharmacies since 1985. The independent Dutch government body National Health Care Institute (Zorginstituut Nederland) is the owner of this database. We used the GIP database to select all medication where the ATC-code starts with 'R03', the mode of administration is 'inhalation' and the year is 2019.

- Exclude the nebulizers since they do not contain propellants and because they are usually not an appropriate alternative for an MDI due to their size and dependency on electricity.
- Label 'soft mist inhalers' as 'DPIs' since they don't contain propellants and may be considered an alternative to MDI.
- Exclude the SABA-SAMA medication, because there are no DPIs containing both SABA and SAMA and they can't be replaced properly. We considered all replacements from MDI to DPI to be acceptable as long as the medication group stays the same and the patient doesn't end up with more inhalers. Because there is no DPI SABA-SAMA available, replacing a MDI SABA-SAMA by a DPI SABA plus a DPI SAMA, would lead to an extra inhaler. This, we did not consider acceptable for replacement. We believed it is not necessary to keep the ATC-code the same during a replacement. E.g., we considered replacing any MDI SABA by any DPI SABA to be acceptable because the medication group did not change.
- Create the following medication groups, allowing replacement within each group or combination of groups: SABA, LABA, ICS, SAMA, SABA-ICS, LABA-ICS and LABA-LAMA-ICS. LAMA and LABA-LAMA are missing from the list of inhalation medication with propellants, as they are always delivered by DPI.

SABA = short-acting beta agonists
SAMA = short-acting muscarinic-antagonists
LABA = long-acting muscarinic-antagonists
LAMA = long-acting muscarinic antagonists
ICS = inhalation corticosteroid

Step 3: Calculate the carbon dioxide impact of replacing MDI by DPI

- Calculate the number of canisters for each specific inhalation medication product. This is done by dividing the total number of DDDs by the number of DDDs in a basic packaging. The number of DDDs in basic packaging is one of the database fields of the GIP database.
- Calculate the carbon dioxide equivalent (CO_2eq.) per type of canister. Do this once using the conversion table from Wilkinson et al.[1] and once using the conversion table from Jeswani & Azapagic.[2] Since both conversion tables deliver different results, we chose to use both tables in order to create a range. Not all types of canisters were mentioned in the two conversion tables. Therefore we had to make some assumptions we marked in the tables (Table 1, Table 2). We based these assumptions on the other data.

Table 1. Conversion table adapted from Wilkinson et al. (2019)

Inhalation medication group	*kilogram CO2 per ca*
ICS	
LABA	
LABA-ICS, Flutiform	
LABA-ICS, all others	
LABA-LAMA-ICS (assumption)	
SABA	
SABA-ICS (assumption)	
SAMA	

[1] Wilkinson AJK, Braggins R, Steinbach I, *et al*. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *BMJ Open* 2019;9:e028763. doi:10.1136/ bmjopen-2018-028763

[2] Jeswani, H. K., & Azapagic, A. (2019). Life cycle environmental impacts of inhalers. *Journal of Cleaner Production*, *237*, [117733]. https://doi.org/10.1016/j.jclepro.2019.117733

Table 2. Conversion table adapted from Yeswani & Azapagic (2019)

Inhalation medication group	*kilogram CO2 per canister*
ICS, brand = Alvesco, ATC = R03BA08	10.946
ICS, all others	15.0475
LABA	13.2535
LABA-ICS, Flutiform	32.0048
LABA-ICS, all others	14.508
LABA-LAMA-ICS (assumption)	19.5
SABA, brand = Airomir_	7.696
SABA, all others	23.374
SABA-ICS (assumption)	19.5
SAMA	14.17

- Calculate the impact of a 69% decrease of MDI use. In 2019 in the Netherlands 49% of inhalation medication DDDs consist of MDIs. We assume this can safely be lowered to 15%, which is equal to a 69% decrease ((49% - 15%)/49%). We have two arguments for this assumption:

1) Current Dutch COPD-guidelines[3] state that children younger than 7 years and patients with at least two exacerbations per year are more dependent on MDIs. Children cannot yet coordinate their breathing well and need an MDI and a spacer. Patients with 'severe' COPD have a low inspiratory flow and therefore require the force of an MDI propellant. We defined 'severe COPD' as requiring at least 42 DDDs of oral corticosteroids per year, which is equal to the treatment of two exacerbations. In our data we observed that 16.3% of MDI DDDs were prescribed for patients who were either younger than 7 years or had severe COPD. If we disregard their MDI DDDs, a replacement of 83.7% is theoretically possible (100% - 16.3%).

[3] Bischoff E, Bouma M, Broekhuizen L, Donkers J, Hallensleben C, De Jong J, Snoeck-Stroband J, In 't Veen JC, Van Vugt S, Wagenaar M. NHG | Nederlands Huisartsen Genootschap (2021) *NHG-richtlijn COPD* [Dutch College of General Practitioners Guideline COPD]. Available: https://richtlijnen.nhg.org/standaarden/COPD [Accessed 19 Apr 2021].

2) In Sweden approximately 10% of inhalation medication consist of MDIs.[4] Assuming Sweden and The Netherlands are comparable in terms of a range of relevant social-epidemiological indicators we believe the latter country should be able to lower their percentage of DDDs delivered by MDIs to 15%.

[4] Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, Crompton GK; Aerosol Drug Management Improvement Team. Retail sales of inhalation devices in European countries: so much for a global policy. Respir Med. 2011 Jul;105(7):1099-103.

Step 4: Calculate the financial impact of replacing MDI by DPI

Calculate the financial impact with two scenarios.

1) Low cost scenario.
   Calculate the costs of all MDI medication and spacers in 2019. Add these costs and multiply by the replacement percentage of 69. These are the current costs. Divide the MDI medication into the following groups or combination of groups: SABA, LABA, ICS, SAMA, SABA-ICS, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 69% of MDI DDDs would be replaced by the low cost DPI in the same group. These are the replacement costs.

2) Average cost scenario.
   Calculate the costs of all MDI medication and spacers in 2019. Add these costs and multiply by the replacement percentage of 69. These are the current costs.
   Divide the MDI medication into the groups: SABA, LABA, ICS, SAMA, SABA-ICS, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 69% of MDI DDDs would be replaced by the weighted average cost of DPI of the same group. These are the replacement costs.

Outcome of steps 1 and 2

Table 3: Inhaler use by diagnosis (nebulisers were excluded, soft mist inhalers were included within DPI).

Type of inhaler	*Patient diagnosis*	*Number of patients/ users **	*Number of DDDS inhalation medication*	*MDIs given for asthma*	*MDIs given for COPD*
DPI	n.a.	468,890	65,361,801		
MDI	n.a.	478,880	51,656,664		
DPI	Asthma	130,700	27,079,696		
MDI	Asthma	165,334	45,608,525	45,608,525	
DPI	COPD	210,595	62,458,264		
MDI	COPD	151,654	49,357,291		49,357,291
DPI	Asthma and COPD	23,198	6,689,357		
MDI	Asthma and COPD	23,549	9,172,019	4,586,010 ** (=50% of 9,172,0	4,586,010 (=50% of 9,172,0
total			317,383,617	50,194,535	53,943,301

It is clear that MDI-use is not very different between patients living with asthma and patients living with COPD.

Table 4. Inhalation medication in the Netherlands 2019

Inhaler type	*Number of patients **	*Number of DDDs ***
Metered-dose (MDI)	819,417	155,794,499
Dry powder (DPI)	833,383	161,589,119
Nebulisers (excluded i further analysis)	30,597	4,886,253
MDI and/or DPI (inclu	1,403,270	317,383,617
MDI and/or DPI and/o nebulisers (total group)	1,409,497	322,269,871

** Users may use different types of inhalers at the same time*

*** Defined daily dose*

In addition 583,704 spacers have been administered to 548,482 (MDI-using) patients, ergo 67% of them received a new, yearly-to-be-replaced, inhaler.

Table 5. Patient groups not eligible for MDI to DPI replacement (nebulisers excluded, soft mist inhalers included within DPI)

Patient group	*Number of patients*	*Their consumption of MDI medication (in DDD)*	*Percentage of their MDI consumption as part of all M consumption*
Severe COPD (COPD and at least 42 DDD prednisone per year)	43,234	20,362,418	13.1%
Younger than 7 years	90,905	5,001,468	3.2%
All others	685,278	130,430,613	83.7%
		155,794,499	100%

Supplementary file: Data analysis protocol

Turning green: the impact of changing to more eco-friendly respiratory healthcare.

A carbon and cost analysis of Dutch prescription data.

Ten Have et al. 2021

Outcome of step 3

Table 6. Number of canisters per group, calculated with product specifications

Inhalation medication group	*Number of MDI DDDs*	*Number of MDI canisters (# DDDs / # DDDs in basic packaging)*
ICS	43,887,810	904,302
LABA	12,019,426	275,312
LABA-ICS	51,797,306	1,642,655
LABA-LAMA-ICS	4,216,418	140,547
SABA	31,745,354	1,269,814
SAMA	7,366,474	220,553
Total	151,032,788	4,453,183

The underlying calculations are on product level, and are not shown here.

Table 7. Reduction of CO_2 equivalents due to theoretical 69% exchange of MDI for DPI

	Using conversion table from Yeswani & Azapagic	*Using conversion table from Wilkinson et al.*
Kilogram CO2 equivalent	75,047,677	83,451,258
69% reduction of MDI use (Kilogram CO2 equivalent)	51,782,897	57,581,368

Outcome of step 4

Table 8. Financial impact of 69% replacement of MDI by DPI

	DDDs of MDI (after exclusion of SABA- and nebulizers)	*Current situation of 69 portion to be replaced*	*Low-cost scenario*	*Average-cost scenario*
Volume in DDD	151,032,789	104,212,624	104,212,624	104,212,624
Medication cost	€ 89,574,691	€ 61,806,537	€ 48,486,061	€ 72,801,318
Cost of spacers	€ 17,882,319	€ 12,338,800	n.a.	n.a.
Total cost	€ 107,457,010	€ 74,145,337	€ 48,486,061	€ 72,801,318
Impact of change			€ 25,659,276 (=positive savings)	€ 1,344,019 (=positive savings)

The low-cost scenario would result in € 25.7 million annual savings, the average-cost scenario would result in € 1.3 million annual savings.

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Title

Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data.

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Abstract

Objectives

Dry powder inhalers (DPIs) and soft mist inhalers have a substantially lower global warming potential than pressurized metered-dose inhalers (pMDIs). To help mitigate climate change, we assessed the potential emission reduction in CO2-equivalents when replacing pMDIs by non-propellant inhalers (NPIs) in Dutch respiratory healthcare, and estimated the associated cost.

Design

We performed a descriptive analysis of prescription data from two national databases of two independent governmental bodies. First, we calculated the number of patients with chronic obstructive pulmonary disease (COPD) and asthma that were using inhalation medication (2020). Second, we calculated the number and total of daily defined doses of pMDIs and NPIs including DPIs and soft mist inhalers, as well as the number of dispensed spacers per patient (2020). Third, we estimated the potential emission reduction in CO2-equivalents if 70% of patients would switch from using pMDIs to using NPIs. Fourth, we performed a budget impact analysis.

Setting

Dutch respiratory healthcare

Primary and secondary outcome measures

The carbon footprint of current inhalation medication and the environmental and financial impact of replacing pMDIs with NPIs.

Results

In 2020, 1.4 million patients used inhalers for COPD or asthma treatment. A total of 364 million defined daily doses from inhalers were dispensed of which 49.6% through pMDIs**.** We estimated that this could be reduced by 70% which would lead to an annual reduction in greenhouse gas emission of 63 million kg. CO2-eq. saving at best EUR 49.1 million per year.

Conclusions

In the Netherlands, substitution of pMDIs to NPIs for eligible patients is theoretically safe and in accordance with medical guidelines, while reducing greenhouse gas emission by 63 million kg. CO2-eq. on average and saving at best EUR 49.1 million per year. This study confirms the potential climate and economic benefit of delivering a more eco-friendly respiratory care.

Strengths and limitations of this study

Strengths

- In countries with national administrative databases on drug use, this type of study quickly provides insight in the current CO2 impact and the potential for improvement in respiratory healthcare.
- This type of study provides insight in the cost/benefit of a large scale shift from propellant to non-propellant inhalers.
- This type of study may be used to monitor implementation strategies to decrease use of propellant inhalers.
- Given availability and reliability of the data, the present analysis could easily be replicated elsewhere which allows for international comparison and aggregation.

Limitations

- Implementation challenges remain underexposed.

INTRODUCTION

Climate change is the greatest global health threat of our times, inflicting a range of ill health outcomes including (re-)emerging zoonoses such as Covid-19, non-communicable diseases and mental health disorders.[1, 2] Paradoxically, the health care industry contributes substantially to global warming. If global health care were a country, it would rank fifth for greenhouse gas emissions and its environmental footprint is substantial.[3, 4] In the Netherlands, the healthcare sector is responsible for 6-7% of the total national CO2-eq. emission.[5] Hence, the Dutch healthcare sector could play a significant role in meeting the national climate policy goals, thereby preserving planetary health and human health that depends on it. Public concerns for health care and for the ecological crises rank high in consecutive opinion surveys of the national statistical office, Statistics Netherlands (CBS).

Among the impactful solutions to deliver sustainable healthcare is the choice of inhaler type to deliver medication to the lungs of patients with asthma, allergies, or chronic obstructive pulmonary disease (COPD). Pressurized metered-dose inhalers (pMDIs) contain propellants known as hydrofluorocarbons (HFCs), potent F-gases that account for 15 megaton CO2-eq. (0.03%) of all greenhouse gas emissions worldwide (RIVM, 2021). In the European Union HFCs will be phased out by two-thirds in 2030 through limiting sale and use of air conditioning and refrigeration equipment. However, their application in metered-dose inhalers is exempted from this regulation.[6] pMDIs contain either the propellant HFC-134a or HFC-227ea. Other commonly used inhalers are dry powder inhalers (DPIs) and soft mist inhalers. For the purpose of this paper we label these as non-propellant inhalers (NPIs). These are as safe and effective in most patients but do not contain greenhouse gases which is why the life cycle assessment of their environmental impact is substantially lower than those of pMDIs.[7]

BOX 1. GLOBAL WARMING POTENTIAL (GWP)

The global warming potential is the heat absorbed by any greenhouse gas in the atmosphere compared to the mass of CO_2. The GWP of CO_2 is 1.0. The GWPs of HFC-134a and HFC-227ea, hydrofluorocarbons used in metered-dose inhalers, are 1,330 and 3,220.

Several studies have assessed the costs and benefits of switching to medication with a lower global warming potential (see Box 1). Wilkinson et al. found considerable reductions in both CO2 emissions and pharmaceutical costs.[8] Janson et al. recommend that "the lower carbon footprint of DPIs should be considered alongside other factors when choosing inhaler devices."[9] In their review, Starup-Hansen et al. recommend to update guidelines: "guidance should consider the potential benefits of advising DPIs as the device of choice in new diagnoses of asthma and COPD as well as the benefits of switching patients currently using pMDIs to DPIs where clinically appropriate."[10] These recommendations have been recently adopted in the

guidelines 'Asthma in adults'[11] and 'COPD'[12] of the Dutch College of General Practitioners. Among other updates, these guidelines contain the same modest, though historical, reference to considering the environmental impact of the medicine of choice for the prescribing physician (see Box 2).

To understand the implications of changing from pMDI to more eco-friendly NPI-use for policy, practice, and patients in settings, we build on the cost and carbon analysis of Wilkinson et al.[8]. In this paper, we calculated the environmental impact of this change in Dutch primary and secondary respiratory healthcare and analyzed the associated pharmaceutical and device costs.

BOX 2. NHG-GUIDELINES 'ASTHMA IN ADULTS' (2020) AND 'COPD' (2021)

One of the criteria in de decision aide for choosing an inhaler device

"A general objection against metered-dose inhalers is that they contain a greenhouse gas with a strong environmental impact."

Note

"Metered-dose inhalers use HFC propellants. The F-gas hydrofluorocarbon does not affect the ozone layer but is a strong greenhouse gas. The environmental impact of 1 inhalation is 25 times larger than a dry powder inhalation. Environmental impact of production, transport and waste processing (..) have not been included."

METHODS

We performed a four-step data analysis of prescription data in order to estimate the carbon equivalent footprint of prescribed inhalers over a one-year period (2020). We determined how much inhalation medication could be attributed to the following patient groups: 1) asthma, 2) COPD, 3) severe COPD and 4) children younger than 7 years of age. Estimations were based on the GIP database (Genees- en hulpmiddelen Informatie Project | Medicines and medical devices Information Project) of the Dutch National Health Care Institute and the DIS database (DBC Informatie Systeem | Diagnosis-Treatment Combination Information system) of the Dutch Healthcare Authority, both independent government bodies residing under the Dutch Ministry of Health, Welfare and Sports. GIP is a representative information system containing data on the use and cost of prescription drugs and medical devices.[13] DIS contains information of all treatment trajectories in Dutch medical specialist care, including pulmonary medicine, mental health care, forensic care and rehabilitation.[14] Health care providers are legally required to deliver these data for policy making and regulation. A *Supplementary File* contains the complete data analysis protocol and additional information regarding methodological details, assumptions and choices made.

First, we calculated the number of patients with asthma or COPD that used inhalation medication in the Netherlands in 2020 by joining diagnoses codes to inhalation medication. Second, we calculated the number of defined daily doses (DDDs) discriminating between pMDIs and NPIs. Nebulizers were excluded from the analysis since they do not contain propellants and due to their size and dependency on electricity, they are not to be considered an alternative to pMDIs for use by patients at home. We included the soft mist inhalers in de NPI group, because they do not contain propellants and may be considered an alternative to pMDIs. Third, we determined the volume of pMDIs that could hypothetically be replaced by NPIs in a safe and medically responsible way. We estimated the size of this volume in DDDs, according to current medical guidelines excluding children younger than 7 years of age and those patients with severe COPD having at least two exacerbations per year. In our data the subgroups 'younger than 7 years' and 'severe COPD' consume 13.6% of the total medication delivered by pMDI. Hence, if we would disregard their pMDI-use, and only replace inhalers of the remaining patients, we could theoretically achieve a 86.4% reduction of pMDI-use. In these two subgroups (younger than 7, severe COPD), it is possible to safely replace pMDIs in inhalation corticosteroid (ICS) maintenance therapy for NPIs, without any negative medical impact. Here, breathing is not hampered during maintenance therapy and an immediate effect of ICS is not required. We nonetheless choose a more conservative estimate of change. We used the frequently stated figure of 10% pMDI-use in Sweden as a proxy, assuming Sweden and The Netherlands are comparable in terms of a variety of social-epidemiological indicators.[15, 16] Hence it is likely that the latter country could approach Sweden's level of NPI-prescription to an again more conservative, putative 15%. From the current level of 49.6% down to 15% pMDI-use equals a 70% reduction, which is considerably less than the previous 86.4% . Based on our data we know how many canisters of each type were prescribed in 2020, and we applied two conversion tables, one published by Wilkinson et al.[8] and the other one by Jeswani & Azapagic.[7] Since they use different resources for quantification we have used a range instead of an average. Finally we calculated the kg. CO2-eq. decrease as a consequence of this substantial 70% reduction in pMDI-use. In the fourth and last step we calculated if this potential replacement could be achieved in a cost-neutral way. By determining both the current costs of medication, spacers and estimated replacement costs we calculated the difference. For the replacement costs we applied two realistic scenarios, one is the low-cost scenario in which pMDIs are replaced by low-cost NPIs. In the second scenario pMDIs are replaced by average-cost NPIs.

Patient and public involvement
No patients involved

RESULTS

In 2020, 1,434,311 patients used inhalation medication in the Netherlands, and they received a total of 364,111,907 defined daily doses (Table 1). In addition 544,544 spacers were administered to 509,650 (pMDI-using) patients meaning that 60% of 856,425 pMDI-using patients could use their inhaler together with a yearly to-be-replaced spacer, as recommended by Dutch medical guidelines.

Table 1. Inhalation medication in the Netherlands 2020

Inhaler type	Number of patients *	Number of DDDs **	% of total DDD use
Pressured Metered-dose (pMDI)	856425	178116715	49.6%
Non-propellant (NPI)	822996	181163394	50.4%
Nebulizers (excluded in further analysis)	24178	4831798	
pMDI and/or NPI (included)	1429677	359280109	100.0%
pMDI and/or NPI and/or nebulizers (total group)	1434311	364111907	

** Users may use different types of inhalers at the same time*

*** Defined daily dose*

After excluding the use of nebulizers, we focused on the group of 1,429,677 patients using pMDI and/or NPI, who were prescribed over 359,280,109 DDDs in 2020 (Table 1). The total amount of medication delivered in 2020 by pMDI is 178,116,715 DDDs. We observed that 49.6% of the medication has been delivered using pMDIs, 50.4% per NPIs (Table 1).

Not all inhalation medication is delivered by both types of inhalers and can be switched. Long-acting muscarinic-antagonists (LAMA) and the combination of long-acting beta agonists with long-acting muscarinic-antagonists (LABA-LAMA) were only available as NPI, the combination of short-acting beta agonists with short-acting muscarinic-antagonists (SABA-SAMA) was only available as pMDI. SABA-ICS has not been analyzed as it was not prescribed.

The number of patients that could hypothetically switch safely to NPIs with the same content would be using 121,043,039 DDDs, equal to 3,543,553 canisters. Here we may safely assume equal bioavailability of pMDIs and NPIs, because their DDD differ which corrects for differences in bioavailability.

Using the Wilkinson's conversion table with "mg HFC per canister", delivers a reduction of 66 million kg. CO2-eq.[8] Using the conversion table from Jeswani & Azapagic yields a reduction of 60 million kg. CO2-eq.[7] The range being 66,028,669 – 60,142,156 kg. CO2-eq. with an average of 63,085,412 kg. CO2-eq. corresponding to 47,977 kg. HFC; HFC-134a for the better part (Figure 1).

FIGURE 1 ABOUT HERE

We calculated if shifting to NPIs could be achieved in a cost-neutral way. We determined both the current costs of medication and spacers, we estimated replacement costs and we calculated the difference. For the replacement costs we applied two realistic scenarios. One is a low-cost scenario in which pMDIs are replaced by low-cost NPIs. In the second scenario pMDIs are replaced by average-cost NPIs in current market share (Table 2).

Table 2. DDD Volumes, costs of medication and spacers

	pMDI-use in 2020, in medication groups: SABA, LABA, ICS, SAMA, LABA-ICS, LABA-SAMA-ICS*	70% of pMDI-use (part that can theoretically be safely replaced)	Replacement of pMDI by low-cost NPI	Replacement by NPI, in current market share
Volume in DDD	172,918,633	121,043,043	121,043,043	121,043,043
Medication cost	€ 129,856,283	€ 90,899,398	€ 54,419,848	€ 107,245,032
Cost of spacers	€ 18,004,187	€ 12,602,931	€ 0	€ 0
Total cost	€ 147,860,470	€ 103,502,329	€ 54,419,848	€ 107,245,032
Impact of replacement			€ 49,082,481 savings	€ 3,742,703 increased costs

*
SABA = short-acting beta agonists | SAMA = short-acting muscarinic-antagonists
LABA = long-acting beta agonists - | LAMA = long-acting muscarinic antagonists
ICS = inhalation corticosteroids

If the percentage of DDD's from pMDI could be reduced from 49.6% to 15% this 70% reduction implies a decrease of 121,043,043 DDDs which equals EUR 103,502,329 (medication + inhalers cost EUR 90,899,398 plus the cost of spacers EUR 12,602,931). Replacing this by

low-cost NPIs, would incur a cost of EUR 54,419,848 saving approximately EUR 49.1 million annually. The average-cost scenario would result in EUR 3.7 million annual added expenses.

DISCUSSION

The healthcare sector needs to decrease greenhouse gas emissions to help mitigate climate change. This may be viewed as a moral and practical obligation in times of climate crisis and the global health emergency it implies.[17] To achieve this, substantiated and medically safe eco-friendly alternatives are necessary. In this study, we assessed the hypothetical impact of converting eligible patients from using pMDIs to using NPIs in the Netherlands, both in terms of greenhouse gas emissions and in cost. With these outcomes we seek to offer insight into the impact of making this change and to inspire health care professionals to act climate responsibly which is congruent with announcements of professional organizations such as the British Thoracic Society,[18] the European Respiratory Society,[19] the International Society for Quality in Health Care,[20] and the US National Academy of Sciences, Engineering, and Medicine.[21]

Our results show that a sizeable reduction in greenhouse gas emissions is attainable in the Netherlands with a readily available eco-friendly alternative. The financial impact of this shift depends on the choice for either a low-cost option or a more expensive option, but we demonstrated a cost reduction is feasible. The estimated cost-saving does not include financial calculations of patient training or potential drawbacks of substitution such as lower adherence leading to increased GP visits or hospital admissions.

These results are in accordance with earlier studies [8, 9, 22] but we were relatively stringent in our eligibility criteria (which patients are able to change safely) and more selective as to what brands to include for the financial impact estimation. Obviously the outcomes refer to Dutch respiratory health care, its specific patient population and medication use.

In estimating the environmental impact of pMDIs, we considered their full amount of propellants. We did not subtract unknown quantities of propellants that may remain in the canister after use, assuming that sooner or later 100% of these gases will be released into the atmosphere. We did not include other environmental impacts of pMDIs nor NPIs, as would have been done in a full life cycle assessment (LCA). LCAs typically include the whole spectrum of production, packaging, distribution, usage, waste, etc. However, pMDIs' global warming effect is mainly caused by their use (95-98%), not by the manufacturing of this class of inhalers.[7, 8] Though NPIs, as opposed to pMDIs, generate much lower GWP, LCAs imply other harmful impacts that eventually should be included in a comparison such as human toxicity, marine eutrophication or fossil depletion.[7] Like Wilkinson, we could not perform a full life cycle assessment due to the lack of reliable LCA-data across all different types of inhalers, spacers,

distribution and manufacturing processes. Since the use of propellants represents a major part of the environmental impact, we nonetheless believe this provides a good start for dealing with these issues.[8]

Our study implies that if medically safe and possible, choosing the medicine or device with the least environmental impact is imperative in times of global climate crisis. This is not just about patients' choice, as may be suggested by NICE's patient decision aid.[23] It could be considered the prescriber's task as well. Therefore it should be integrated in medical guidelines and standards as part of health care quality improvement trajectories much like Mortimer et al. have elegantly proposed and practiced.[24] This should not affect the established fact that suitable patient training and monitoring of inhalation techniques are a sine qua non for effective inhaler use for all a patients, especially for children.[25, 26] In the Netherlands, general practitioners recently updated their guidelines on the management of asthma and COPD, and included a recommendation to consider the environmental impact of the medicine of choice (see Textbox 2). In view of the health emergency represented by the climate crisis we recommend that pulmonologists also consider to update national and local guidelines and appreciate the potential benefits of advising green inhalers as the device of choice in new diagnostics of asthma and COPD and the benefits of resetting patients currently using pMDIs to NPIs if safe and possible. In 2019 Belgian pulmonologists recommended the use of DPIs to lung patients not just because they can deliver better treatment results for asthma and COPD but also because they are "far less damaging to the environment than traditional propellant driven aerosols."[27]

Evidently, the chosen medication should be fitting for the individual patient. It is beyond the scope of this study to include all specific circumstances in which patients cannot use NPIs. Since daily use and emergency use are quite different, there have been reservations about DPIs in case of exacerbations especially since both the expiratory flow and the inspiratory ('trapped air') flow of breath are obstructed leading to patients' preference for pMDIs in such circumstances. In Sweden soft mist inhalers are recently used more often in such cases because they require minimal inspiratory power. Wilkinson et al. referring to a data analysis of the NHS Business Services Authority, suggest that in England "clinicians believe the vast majority of patients can use a DPI effectively."[8]

Apart from climate and economic benefits we identified more advantages of replacing pMDIs with NPIs as suggested by research and practice (Table 3).

Table 3. Plausible advantages of replacing pMDIs with DPIs.

Plausible advantages	References (if present)
Less critical errors are made using DPIs as compared to pMDIs.	Chrystyn H, van der Palen J, Sharma R, Barnes N, Delafont B, Mahajan A, Thomas M. Device errors in asthma and COPD: systematic literature review and meta-analysis. NPJ Prim Care Respir Med. 2017 Apr 3;27(1):22.
Sometimes pMDIs are used when empty, which may lead to poor disease control and less quality of life.	Conner JB, Buck PO. Improving asthma management: the case for mandatory inclusion of dose counters on all rescue bronchodilators. J Asthma. 2013 Aug;50(6):658-63. doi: 10.3109/02770903.2013.789056. Epub 2013 Apr 29. Tsangarides A, Wilkinson A, Mir F. Disadvantages of salbutamol pressurised metered-dose inhalers (pMDIs). *Thorax* 2018;73:A193-A194.
Some pMDIs are unknowingly considered empty and are disposed of leading to unnecessary costs.	Holt S, Holt A, Weatherall M, Masoli M, Beasley R. Metered-dose inhalers: a need for dose counters. Respirology (Carlton, Vic.). 2005 Jan;10(1):105-106.
Following Dutch clinical guidelines, pMDI-users should yearly receive a new spacer. During 2020 however, only 60% of pMDI-using patients received it which implies suboptimal quality of care.	
Changing to DPI may improve guideline adherence because use of a spacer is not required for DPI.	
Use of DPI requires no spacers and consequently does at least not generate non reusable plastics	

The present study does not discuss implementation questions, or possible (dis-)advantages of pMDI or NPI use. We have assumed a 100% implementation to determine the maximum impact. What level of implementation can be achieved in health care practice is yet unknown and depends on a range of contextual factors, e.g. does the patient perceive benefits or harm. But if one could estimate what level of implementation can be achieved in practice, the actual impact could easily be calculated with the data from the present paper. It is certainly useful to address the preferences and prejudices of patients and professionals and we know that citizens, patients and professionals are increasingly willing to choose eco-friendly alternatives but there

is no knowledge on this specific shift from pMDIs to NPIs.[28-30] Next to that, while some practical (dis-)advantages of both pMDIs and NPIs are known we recommend explaining these to patients similar to the NICE decision aid as well as to professionals.[23, 31] For example, most pMDIs do not have dose-counters. While all DPIs have a counter they do not necessarily prevent using an empty device. Without a dose-counter it may be hard to know how many doses are left in the device. Unknowingly using empty pMDIs could lead to avoidable exacerbations or even avoidable hospital admissions. Unknowingly replacing pMDIs that still contain medication would incur unnecessary cost.[32] Adherence to inhalation instructions may be an issue when it comes to changing, but this is already an issue e.g., not every patient with an pMDI uses the recommended, though bulky, spacer. Also, adherence to inhalation medication therapy should be supported and promoted by repeated inhalation instruction.[33] Switching without sufficient instruction may result in uncontrolled, exacerbations and increased use of health care services. Uniformity of the devices in case of multiple inhaler use is relevant here. Such questions pertain to responsible implementation, a subject we address in the follow-up study, that has already begun.

The pharmaceutical industry meanwhile continues to develop and study inhalers with lower climate impacts. And new propellants will enter the market. For patients who are dependent on pMDIs, this is meaningful. Given that these developments have not yet entered the market and knowledge of these is still limited, we will not elaborate on this matter. Research should nonetheless include more green metrics into their output and outcome parameters. This would enable meta-analyses and evidence-based climate-responsible innovation in health care.

CONCLUSIONS

Large scale replacement of pMDIs with NPIs would have a substantial climate impact in respiratory healthcare. In 2020 about 1.4 million patients using pMDI and/or NPI, were prescribed over 364 million DDDs. The use of pMDIs is more or less equally prevalent among patients with COPD and patients with asthma. Half (49.6%) of the medication has been delivered through pMDIs that have a relatively high global warming potential. The percentage of NPI-delivered inhalation medication that can safely be replaced is estimated to be 70%, resulting in an environmental health benefit of 63,085,412

kg. CO_2-eq. on average, which equals the carbon dioxide emission of just over 8400 Dutch households. This shift could be achieved with low budgetary risk. In the low-cost scenario it may even lead to a cost reduction of approximately EUR 49.1 million per year in Dutch respiratory health care. The average-cost scenario would result in EUR 3.7 million annual added costs while still reducing greenhouse gas emission.

Figure 1. Environmental impact (in kg.CO2-equivalents) of a hypothetical replacement of pMDIs in The Netherlands.

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Contributors

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Data availability statement

Both databases used for this article are publicly accessible. Commercially sensitive information related to brand names cannot be made available.

Author note

All authors meet the required criteria for authorship. All of them contributed substantially to the conception and design of the study; to the analysis or interpretation of data; and to drafting the work as well as improving/revising it; that includes the final approval of the version to be (pre-)published and (re-)submitted. They all agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary File

Data analysis protocol (Appendix)

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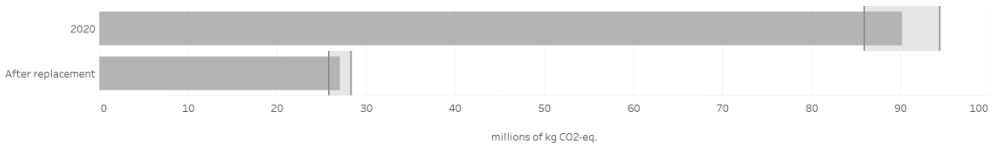

Fig. 1 Environmental impact (in kg. CO2-equivalents) of a hypothetical replacement of pMDIs in The Netherlands.

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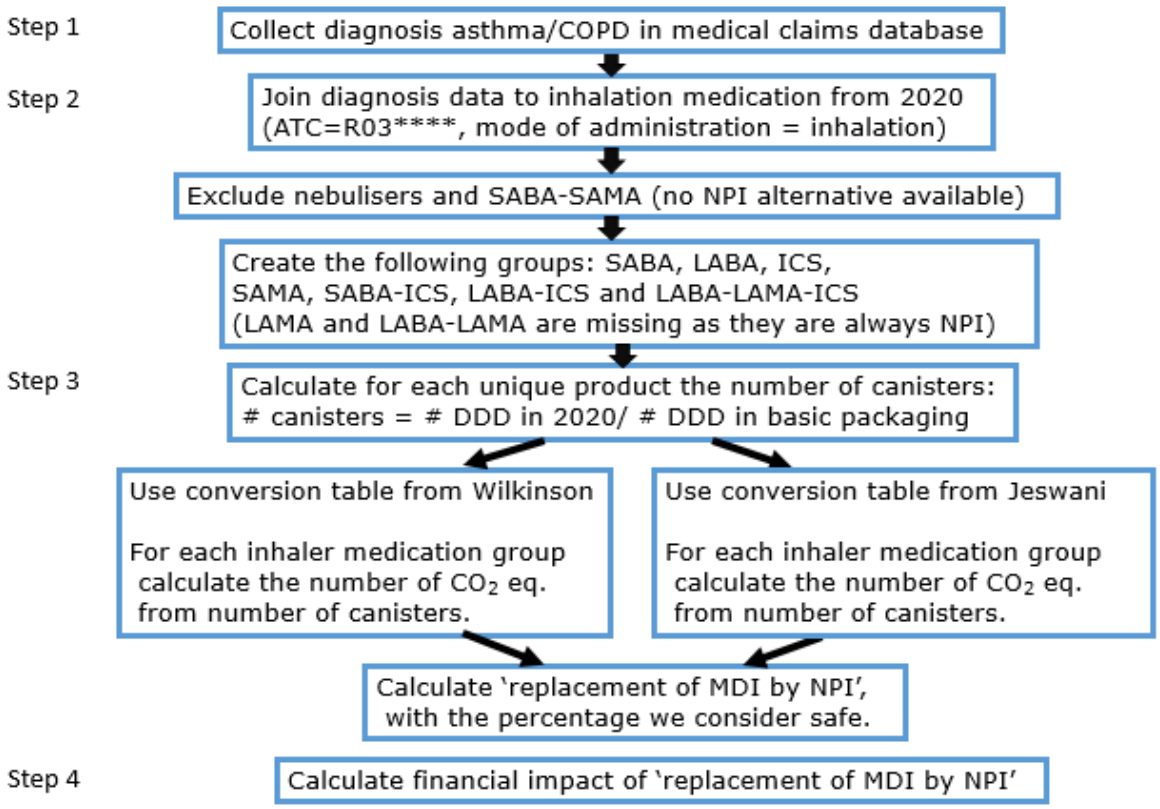
SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Introduction

We calculate the impact of replacing pressurized metered-dose inhalers (pMDIs) by non-propellant inhalers (NPIs), a group consisting of both dry powder inhalers (DPIs) and soft mist inhalers, on greenhouse gas emissions in Dutch respiratory healthcare. The major steps of our method are shown in Figure 1.

Figure 1. Steps to calculate the impact of conversion of pMDI to NPI



Our data-analysis protocol is:

Step 1: Collect diagnoses asthma/COPD from medical claims database

Use the DIS database (DBC Informatie Systeem | Diagnosis-Treatment Combination Information system) to collect the identifiers and diagnoses of patients that received care for asthma or COPD between 2012 and 2020. The DIS database is a medical claims database covering all medical care delivered to Dutch citizens, including private health

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care. The independent government body Dutch Health Care Authority (Nederlandse Zorgautoriteit) owns this database. The reason for this initial step is to find out how many pMDI DDDs[1] were prescribed for patients with severe COPD, as guidelines do not consider them eligible for DPI. Also, we wanted to know how pMDIs are distributed between asthma and COPD. The DIS database does not contain all primary care diagnoses.

Step 2: Join these diagnoses to the inhalation medication prescribed in 2020

The GIP database (Genees- en hulpmiddelen Informatie Project | Medicines and medical devices Information Project) contains all prescriptions of all Dutch citizens from pharmacies since about 1985. The Dutch National Health Care Institute (Zorginstituut Nederland) is the owner of this database. Use the GIP database to select all medication where the ATC-code starts with 'R03', the mode of administration is 'inhalation' and the year is 2020. Increase all numbers with 3%, because a few small health insurance companies do not deliver claims data. These missing data represent 3% of the claims volume.

Exclude the nebulizers since they don't contain propellants and because they are usually not an appropriate alternative for a pMDI due to their size and dependency on electrical energy.

Label 'soft mist inhalers' and 'DPIs' as non-propellant inhalers (NPIs) since they do not contain propellants and may be considered an alternative to pMDI.

Exclude the SABA-SAMA medication, because there are no NPIs containing both SABA and SAMA and they can't be replaced properly. We considered all replacements from pMDI to NPI to be acceptable as long as the medication group stays the same and the patient doesn't end up with more inhalers. Because there is no NPI SABA-SAMA available, replacing a pMDI SABA-SAMA by a NPI SABA plus a NPI SAMA, would lead to an extra inhaler. This, we did not consider acceptable for replacement. We believed it is not necessary to keep the ATC-code the same during a replacement. E.g., we considered replacing any pMDI SABA by any NPI SABA to be acceptable, since the medication group remained unchanged.

[1] The Defined Daily Dose (DDD) is an international technical unit of measuring drug consumption defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (source: https://www.who.int/tools/atc-ddd-toolkit/about-ddd).

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Create the following medication groups, allowing replacement within each group: SABA, LABA, ICS, SAMA, SABA-ICS, LABA-ICS and LABA-LAMA-ICS. LAMA and LABA-LAMA are missing from the list of inhalation medication with propellants, as they are always delivered by NPI.

Step 3: Calculate the carbon dioxide impact of replacement of pMDI by NPI

Calculate the number of canisters for each specific inhalation medication product. The number of DDDs in basic packaging is one of the database fields of the GIP database.

Calculate the carbon dioxide equivalent (CO_2 eq.) per type of canister. Do this once by using the conversion table from Wilkinson et al.[2] and once by using the conversion table from Jeswani & Azapagic.[3] Because the two conversion tables deliver different results, we choose to use both tables in order to create a range. Not all types of canisters were mentioned in the two conversion tables. Therefore we added some assumptions to the tables and marked them. We based these assumptions on the other data.

Table 1. Conversion table adapted from Wilkinson et al. (2019)

Inhalation medication group	*kilogram CO2 per canister*
ICS	20.4
LABA	15.6
LABA-ICS, Flutiform	36.5
LABA-ICS, all others	19.6
LABA-LAMA-ICS (assumption)	19.6
SABA	17.2
SABA-ICS (assumption)	19.6
SAMA	14.3

[2] Wilkinson AJK, Braggins R, Steinbach I, *et al*. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *BMJ Open* 2019;9:e028763. doi:10.1136/ bmjopen-2018-028763

[3] Jeswani, H. K., & Azapagic, A. (2019). Life cycle environmental impacts of inhalers. *Journal of Cleaner Production*, *237*, [117733]. https://doi.org/10.1016/j.jclepro.2019.117733

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Table 2. Conversion table adapted from Yeswani & Azapagic (2019)

Inhalation medication group	*kilogram CO2 per canister*
ICS, brand = Alvesco, ATC = R03BA08	10.946
ICS, all others	14,5
LABA	15.6
LABA-ICS, Flutiform	32.0048
LABA-ICS, all others	14.508
LABA-LAMA-ICS (assumption)	14.5
SABA, brand = Airomir_	7.696
SABA, all others	23.374
SABA-ICS (assumption)	14.5
SAMA	14.17

Calculate the impact of a 70% decrease of pMDI use. In 2020 in the Netherlands 49.6% of inhalation medication DDDs consist of pMDIs. We assume this can safely be lowered to 15%, which is equal to a 70% decrease ((49.6% - 15%)/49.6%). We have two arguments for this assumption:

1) Current Dutch COPD-guidelines[4] state that children younger than 7 years and patients with severe COPD are more dependent on pMDIs. Children cannot yet coordinate their breathing well and need an pMDI and a spacer, and patients with 'severe' COPD have a low inspiratory flow and therefore require the force of a pMDI propellant. We defined 'severe COPD' as COPD requiring at least 42 DDDs of oral corticosteroids per year, which is equal to two treatments of exacerbations. In our data we observed that 13.6% of pMDI DDDs were prescribed for patients who were either younger than 7 years or had severe COPD. If we leave their pMDI DDDs untouched, a replacement of 86.4% would theoretically be possible (100 - 13.6)/100).

[4] Bischoff E, Bouma M, Broekhuizen L, Donkers J, Hallensleben C, De Jong J, Snoeck-Stroband J, In 't Veen JC, Van Vugt S, Wagenaar M. NHG | Nederlands Huisartsen Genootschap (2021) *NHG-richtlijn COPD* [Dutch College of General Practitioners Guideline COPD]. Available: https://richtlijnen.nhg.org/standaarden/COPD [Accessed 19 Apr 2021].

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2) In Sweden approximately 10% of inhalation medication consists of pMDIs. [5] If we assume that Sweden and The Netherlands are quite comparable in terms of a variety of social-epidemiological indicators we believe the latter country should be able to lower their percentage of DDDs delivered by pMDIs to 15%.

Step 4: Calculate the financial impact or replacement from pMDI to NPI

Calculate the financial impact with two scenario's:

1) Low-cost scenario
   Calculate the costs of all pMDI medication and spacers in 2020. Add these costs and multiply by the replacement percentage of 70. These are the current costs.
   Divide the pMDI medication into the groups: SABA, LABA, ICS, SAMA, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 70% of pMDI DDDs would be replaced by the low cost NPI in the same group. These are the replacement costs.

2) Average-cost scenario
   Calculate the costs of all pMDI medication and spacers in 2020. Add these costs and multiply by the replacement percentage of 70. These are the current costs.
   Divide the pMDI medication into the groups: SABA, LABA, ICS, SAMA, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 70% of pMDI DDDs would be replaced by the weighted average cost of NPI of the same group. These are the replacement costs.

[5] Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, Crompton GK; Aerosol Drug Management Improvement Team. Retail sales of inhalation devices in European countries: so much for a global policy. Respir Med. 2011 Jul;105(7):1099-103.

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Outcome of steps 1 and 2

Table 3: Inhaler use by diagnosis (nebulizers were excluded, soft mist inhalers were included within DPI).

Type of inhaler	*Patient has diagnosis*	*Number of patients/ users **	*Number of DDDS of inhalation medication*	*pMDIs prescribed for asthma*	*pMDIs prescribed for COPD*
pMDI	n.a.	513,764	65,564,970		
NPI	n.a.	471,340	74,683,448		
pMDI	Asthma	164,684	49,196,500	49,196,500	
NPI	Asthma	123,875	29,019,163		
pMDI	COPD	156,281	54,771,181		54,771,181
NPI	COPD	206,782	70,717,311		
pMDI	Asthma and COPD	21,697	8,584,064	4,292,032	4,292,032
NPI	Asthma and COPD	20,999	6,743,472		
Total			359,280,109	53,488,532	59,063,213

It is clear that pMDI use is not very different between patients with asthma and patients with COPD. It is also clear that primary care diagnoses of asthma and COPD are missing.

Table 4. Inhalation medication in the Netherlands 2020

Inhaler type	Number of patients *	Number of DDDs **
Pressured Metered-dose (pMDI)	856,425	178,116,715
Non-propellant (NPI)	822,996	181,163,394
Nebulizers (excluded in further analysis)	24,178	4,831,798
pMDI and/or NPI (included)	1,429,677	359,280,109
pMDI and/or NPI and/or nebulizers (total group)	1,434,311	364,111,907

* *Patients may use different types of inhalers at the same time*
** *Defined daily dose*

In addition 544544 spacers have been issued to 509650 (pMDI using) patients, so 60% of the pMDI-users received a new, yearly-to-be-replaced, inhaler.

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Table 5. Patient groups not eligible for pMDI to NPI replacement (nebulizers were excluded)

Patient group	*Number of patients*	*Their consumption of pMDI medication (in DDD)*	*Percentage of their pMDI consumption as part of all pMDI consumption*
Severe COPD (COPD and at least 42 DDD prednisone per year)	47,068	19,532,565	11.0%
Younger than 7 years of age	75,948	4,583,947	2.6%
All others	1,311,295	154,000,203	86.5%
		178,116,715	100%

Outcome of step 3

Table 6. Number of canisters per group, calculated with product specifications

Inhalation medication group	*Number of pMDI DDDs*	*Number of pMDI canisters*
ICS	48,206,256	941,550
LABA	12,145,621	278,581
LABA-ICS	56,693,829	1,759,025
LABA-LAMA-ICS	7,066,541	235,406
SABA	38,408,864	1,536,355
SABA-ICS	0	0
SAMA	10,397,516	311,303
Total	172,918,627	5,062,219

The underlying calculations are at product level, and are not shown here.

Table 7. Reduction of CO_2 equivalents due to theoretical 70% exchange of pMDI for NPI

	Using conversion table from Yeswani	*Using conversion table from Wilkinson*
Kilogram CO2 equivalent	85,917,365	94,326,670
70% reduction of pMDI use (in Kilogram CO2 equivalent)	60,142,156	66,028,669

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Outcome of step 4

Table 8. Financial impact of 70% replacement of pMDI to NPI

	DDDs of pMDI, which can be replaced	*Portion of pMDI to be replaced (70%)*	*Low-cost scenario*	*Average-cost scenario*
Volume in DDD	172,918,633	121,043,043	121,043,043	121,043,043
Medication cost	€ 129,856,283	€ 90,899,398	€ 54,419,848	€ 107,245,032
Cost of spacers	€ 18,004,187	€ 12,602,931	€ 0	€ 0
Total cost	€ 147,860,470	€ 103,502,329	€ 54,419,848	€ 107,245,032
Impact of replacement			€ 49,082,481 savings	€ 3,742,703 increased cost

The low-cost scenario would result in €49.1 million annual savings, the average-cost scenario would result in € 3.7 million annual extra expenditure.