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Original Research

Short-acting β_2-agonists (SABA) overuse in asthma and patients' perceptions for this behavior

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ABSTRACT

Background: Short-acting β_2-agonists (SABA) overuse is associated with poor asthma control. The Global Initiative for Asthma (GINA) 2019-updated strategy report has therefore taken a paradigm shift in reliever therapy recommendations.
Objectives: (I) To investigate the status of SABA overuse and medication dispensing patters in asthma in the Netherlands (II) validate dispensing data for SABA overuse identification and (III) understand patients' perspectives towards this SABA-taking behavior to inform future improvement strategies.
Methods: An annually repeated cross-sectional study was conducted from 2017 to 2021 using pharmacy dispensing data in a real-world setting, including asthma patients aged 18–45 with ≥1 inhaler. A following qualitative study was performed in identified SABA overusing patients with a questionnaire and semi-structured interviews, supported by theoretical frameworks.
Results: Dispensing data was available from 87 % of all community pharmacies (n = 1994) in 2017 and 95 % (n = 2005) in 2021. SABA overuse prevalence was constant for the five study-years with 20.6 % (±0.5 %). Increased ICS-formoterol and decreased SABA dispenses were observed in starters of inhalation therapy in 2021. 53 asthma patients completed the questionnaire of whom 43 patients confirmed SABA overuse, generating a positive predictive value of 81 %. Key behavioral drivers covered 7 themes regarding capability (knowledge; skills; memory, attention and decision process) motivation (emotion; beliefs about-capabilities; consequences) and opportunity (environmental context).
Conclusion: SABA overuse remains in one-fifth of asthma patients across the Netherlands, requiring careful attention from healthcare professionals. Dispensing data is a valid measure for SABA overuse in a clinical setting, facilitating patient selection. To meet patients' varied supporting needs, integration of tailored behavioral interventions is essential.

1. Introduction

Asthma is a chronic respiratory condition affecting over 300 million people worldwide [1,2]. Despite the availability of effective pharmacotherapy, poor asthma control remains [3–6]. A common attributable factor is overuse of short-acting β_2-agonists (SABA) for symptom relief, which is often paralleled by underuse of inhalation corticosteroids (ICS) to prevent asthma attacks [7]. SABA overuse is alarming as it does not address the underlying inflammatory pathophysiology of asthma [8,9]. Moreover, inappropriate use of SABA can adversely increase the risk of subsequent exacerbations, hospitalization and mortality [10–12]. Accordingly, the Global Initiative for Asthma (GINA) 2019-updated strategy report has taken a paradigm shift from SABA monotherapy to anti-inflammatory reliever therapy comprising of ICS tethered to formoterol as fast-onset long-acting β_2-agonist (LABA) [13]. Though, implementation of clinical practice guidelines requires awareness and acceptance from healthcare professionals (HCPs) and patients [3,14].

SABA overuse is recognized as potential warning sign of poor asthma

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control. Close monitoring has therefore been advocated, flagging patients who may benefit from treatment reviews [3]. Pharmacy dispensing data is a commonly applied proxy measure to identify and quantify medication use including the impact of interventions in a real-world setting at both a patient and population-level [15–17]. Consequently, routinely collected dispensing data enables HCPs to regularly perform medication safety assessments and reviews to optimize pharmacotherapy for individual patients [18–20]. However, the extent to which pharmacy dispensing data accurately reflects actual SABA overuse has not yet been assessed. Stockpiling of inhalers is often considered a plausible possibility inflating SABA overuse estimates [21,22].

Moreover, self-management of inhalation therapy is essential to achieve optimal asthma control. This is greatly influenced by complex inter-related perceptions of patients regarding asthma and its pharmacotherapy [3,23–25]. The primary care setting is key in continuous self-management support and shared treatment decision-making, involving inhalation instructions and education programs [3,25,26]. Yet, optimal self-management support requires a thorough understanding of the multifaceted patient-drivers to SABA overuse in asthma patients. Current interventions are predominantly based on implicit commonsense models, a one-size fits-all approach without underpinning theories and an incomplete range of possible influences. Application of the theoretical domains framework (TDF) can identify individual behavioral determinants based on psychological theories aimed at behavior change [27,28]. Complementary, TDF-domains provide a granular understanding, elucidating details of fundamental overarching constitutes 'capability', 'opportunity' and 'motivation' which interact to generate 'behavior' (COM-B model) [29].

Hence, the present study aims to investigate the status of SABA overuse and medication patterns in asthma patients in the Netherlands; to validate pharmacy dispensing data as proxy measure for SABA overuse; and to explore patients' perceptions for this SABA-taking behavior based on the TDF and COM-B model.

2. Methods

2.1. Study design and data source

This study comprised of two components utilizing pharmacy dispensing data in the Netherlands: (1) an annually repeated cross-sectional quantitative study to describe SABA overuse and medication patterns in asthma on a population-level from 2017 to 2021; (2) a qualitative study to validate the dispensing algorithm for the identification of SABA overuse in asthma and explore patients' perceptions for this SABA-taking behavior, obtained by a self-report questionnaire and subsequent semi-structured interviews (see Supplementary Material A for the study procedures flowchart). Information on medication dispenses was retrieved from the Dutch Foundation of Pharmaceutical Statistics (SFK), which collects routine dispensing data from more than 98 % of approximately 2000 community pharmacies [30]. Within pharmacies, dispensing data are aggregated on patient-level in the electronic information systems, identifiable by unique patient identifiers (UPIs). These data contain information on medication dispensed specified with Anatomical Therapeutic Chemical (ATC) codes including date of supply, quantity supplied and the defined daily dose (DDD) [31]. Information on clinical diagnosis is not registered to SFK.

The Medical Ethics Committee (MEC) of Leiden University Medical Center (LUMC) declared that the Medical Research Involving Human Subjects Act did not apply to this study (N21.095). Approval was obtained from the scientific review committee of the department of Clinical Pharmacy and Toxicology of the LUMC and advisory board of SFK. This study was conducted in accordance with the Declaration of Helsinki. Dispensing data were not retraceable to patients or pharmacies by the researchers. Accordingly, informed consent was not warranted for use of data from SFK, compliant with legislation on non-interventional studies coherent with Directive 2001/20/EC and the Dutch legislation [32]. Written informed consent was obtained from participants prior to enrollment in the qualitative study.

2.2. Quantitative study: SABA overuse and medication patterns

2.2.1. Study population

Per calendar year in the study period, community pharmacies were eligible for inclusion when a complete dispensing history was provided including UPIs. A complete dispensing history of the previous year was additionally required to differentiate starters from prevalent users of inhalation therapy. Conventionally, starters were defined as patients with a first dispensing in the calendar year without a previous dispensing within the complete ATC group R03 for respiratory diseases in the prior 12-months; including a generated code stating a first dispensing fee was charged, as registered in community pharmacies [33]. Correspondingly, pharmacies with complete data for two consecutive calendar years from 2016 to 2021 were included.

Asthma patients within the included pharmacies per calendar year were selected, defined as individuals aged 18–45 with ≥1 inhaler dispensing according to the ATC R03 codes: SABA (R03AC), LABA (R03AC), long-acting muscarinic antagonists (LAMA; R03BB) and/or ICS (R03BA, R03AK, R03AL) (see Supplementary Material B) [34]. Starters with 1 SABA inhaler dispensing without other ATC R03 dispenses within a calendar year were excluded, ascribed to uncertainty in asthma diagnosis [26]. The lower age cut-off was applied due to differences in asthma management for children and the upper age was chosen to decrease the risk of including chronic obstructive pulmonary disease (COPD) patients. Data from patients visiting multiple pharmacies were merged to one anonymous patient code by SFK, based on UPIs. A 12-month reporting period was applied to reduce prevalence bias as consequence of seasonal variation in asthma.

2.2.2. Study measures

Included patients were considered SABA user if ≥1 SABA inhaler dispensing. SABA overuse assessment required ≥2 SABA inhaler dispenses and was defined as ≥2 inhalations per week (>104 DDD per year) [3,26]. The extent of SABA overuse was expressed as the average inhalations per day, computed by the division of number of inhalations per dispensing by the difference in days between dispenses. SABA monotherapy was defined as receiving no other ATC R03 dispenses. Concomitant ICS therapy was defined by the presence of ≥1 ICS inhaler dispensing. To estimate ICS adherence, the proportion of days covered (PDC) was calculated as the average number of days covered by ICS inhaler dispenses according to the prescribed daily dose in relation to the number of days in the calendar year (from the first day of dispensing). Adherent patients were stated as PDC ≥80 % [33]. For medication pattern assessment, starters on ICS-formoterol were defined as patients who received ≥1 ICS-formoterol (without SABA) inhaler dispensing. Exacerbations were established by ≥1 predniso(lo)ne dispensing as short-term oral corticosteroid (OCS) course (see Supplementary Material B) [6,34]. All study measures were calculated on patient-level per calendar year (see Supplementary Material C).

2.3. Qualitative study: dispensing validation and patients' perceptions

2.3.1. Study population

To validate the dispensing algorithm for the identification of SABA overuse and to provide insight into patient-drivers for this SABA-taking behavior, 50 community pharmacies from the Leiden University internship database in the Netherlands were invited to each select and recruit 12 asthma patients with potential SABA overuse (≥2 inhalations per week) in November 2021. Patients aged ≥18 and identified with SABA overuse were selected within participating pharmacies. SABA overuse assessment was performed on patients with ≥2 SABA inhaler dispenses in the prior 6-months (April–October 2021) conducted by SFK

(see Supplementary Material C). Concomitant ICS use was established as ≥1 ICS inhaler dispensing in the prior 12-months (October 2020–October 2021). Purposive sampling ensured including SABA overusing patients with and without concomitant ICS therapy and various extents of calculated SABA inhalations per week. Eligible patients were screened for asthma within pharmacy information systems. Exclusion criteria were: COPD diagnosis, other lung diseases, cognitive impairments, lack of digital skills, internet access and the incapability to speak, read and write the Dutch language. The recruitment of patients was conducted by phone or through pharmacy visits.

2.3.2. Data-collection

Participating patients were invited to complete an online self-report questionnaire on their SABA use. The questionnaire contained 50 close-ended and 11 open-ended questions related to patient demographics, actual SABA use (average inhalations per week), ICS adherence, perspectives on asthma and inhalation therapy, exacerbations, asthma-related healthcare utilization and hospital admissions. The questionnaire was developed based on empirical evidence acquired by a systematic literature review in which preconceived items were identified and allocated to TDF-domains [27]. Formulated statements were framed as negative or positive connotations to limit social-desirability bias, rated on a five-point Likert scale ranging from complete disagreement to complete agreement. Content and face validity of the questionnaire was performed by the research team and an asthma patient assessing the relevance, readability, feasibility and comprehensiveness of the formulated questions. The final questionnaire (see Supplementary Material D) was built within Castor Electronic Data Capture (EDC) to safeguard collected data in LUMC surroundings, compliant with General Data Protection Regulation (GDPR).

Furthermore, patients were invited to participate in a semi-structured interview to elaborate on the filled-out questionnaire through an open dialogue approach, conducted by phone. An interview topic guide (see Supplementary Material E) was constructed based on insights of TDF-related topic guides from previous studies, to elicit patients to provide overt information on components of the questionnaire [35,36]. Interviews were conducted in Dutch by two researchers (who did not have any prior contact with participants), recorded, transcribed verbatim and safeguarded within LUMC surroundings.

2.4. Data analyses

Descriptive statistics were used to summarize patient characteristics and medication use, using SPSS statistical software (version 26.0 IBM, NY, USA).

To enable comparisons between calendar years within the quantitative study, patient numbers from the included pharmacies were extrapolated to the total number of community pharmacies in the Netherlands for each calendar year. Proportion of SABA overusing patients were calculated in relation to all SABA and all inhalation therapy users in the study population. Dispensing patterns of starters on SABA monotherapy, SABA with concomitant ICS and ICS-formoterol (without SABA) were displayed in relation to all starters on inhalation therapy.

A positive predictive value (PPV) was calculated in the qualitative study, to validate the algorithm on dispensing data as proxy measure for the identification of SABA overusing patients. This was determined with the conformation of actual SABA overuse on the questionnaire by patients identified as SABA overuser. Responses on Likert scales of actual SABA overusing patients were summarized into three groups: ‘agreed on’, ‘neutral’ or ‘disagreed on’. Grounded theory was employed by three independent researchers during thematic analysis of qualitative data collected from the questionnaire and interview transcripts. Data was coded and organized into TDF-domains and constitutes of the COM-B model as overarching structure (see Supplementary Material F).

3. Results

3.1. Quantitative study: SABA overuse and medication patterns

Pharmacy dispensing data was available from 1727 community pharmacies (86.6 %) in 2017 and 1906 pharmacies (95.1 %) in 2021 (Fig. 1). A total of 267,845 patients aged 18–45 with asthma inhaler dispenses were included in 2017 which declined to 252,272 patients in 2021. A mean of 164,071 (±5706) patients were classified with SABA inhaler dispenses per calendar year during this five-year period, representing 63.4 % (±1.5 %) of the total study population; 20.1 % (±0.72 %) on SABA monotherapy and 42.7 % (±1.1 %) on SABA with concomitant ICS therapy. ICS-formoterol inhaler dispenses (without SABA) were identified in 16.7 % (±1.9 %) of patients.

3.1.1. SABA overuse

The prevalence of SABA overuse was constant during the five-year period with a mean of 20.6 % (±0.5 %) in relation to the total study population and 32.6 % (±0.7 %) of all SABA users (Table 1). Mean SABA overuse was 1.06 (±6.24) inhalations per day; 51.4 % (±0.46 %) of patients were classified as 2–3 inhalations per week, 23.0 % (±0.11 %) as 4–5 inhalations per week, 10.6 % (±0.19 %) as 6–7 inhalations per week, 4.72 % (±0.08 %) as 8–9 inhalations per week and 10.2 % (±0.29 %) as ≥10 inhalations per week. OCS courses were dispensed in 14.5 % (±2.2 %) of SABA overusing patients.

Concomitant ICS inhaler dispenses were present in 67 % (±1.6 %) of SABA overusing patients and remained constant during the five-year period. Mean PDC for ICS was 69.4 % (±29.6 %) of which 46.3 % (±1.1 %) of patients were considered adherent.

3.1.2. Medication dispensing patterns

From all starters on inhalation therapy, a slight increase in SABA monotherapy dispenses was observed from 12.9 % in 2017 to 17.1 % in 2020, followed by a decrease to 15.0 % in 2021 (Fig. 2). Starters on SABA with concomitant ICS (any) inhaler dispenses remained similar from 2017 to 2020 with a mean of 41.9 % (±0.4 %), followed by a slight decrease to 39.6 % in 2021. Adversely, starters on ICS-formoterol inhaler dispenses remained constant with a mean of 17.2 % (±0.9 %) from 2017 to 2020, followed by an increase to 23.0 % in 2021.

3.2. Qualitative study: dispensing validation and patients’ perceptions

Out of 319 eligible asthma patients identified with SABA overuse who were invited from 30 of the 50 pharmacies (60 %), 56 patients (17.6 %) were enrolled and completed the questionnaire (Fig. 1). Three patients were excluded due to other lung diseases notified in the questionnaire. Of the remaining 53 patients, SABA overuse was confirmed in 43 patients, generating a PPV of 81.1 % for the identification of SABA overuse in asthma with the applied dispensing algorithm (see Supplementary Material G).

Perceptions of these 43 patients regarding their SABA overuse behavior were explored. Their demographic characteristics are presented in Table 2. The mean age (±SD) was 48.5 (±13.9) of which 60.5 % were female. Asthma diagnosis existed for over more than 10 years in 79.1 % of patients. Non-allergic asthma was reported in 60.5 % of patients, exercise-induced asthma in 39.5 % and/or allergic asthma in 46.5 %. Overall, 51.2 % of patients deemed their asthma controlled, 41.9 % as partly-controlled and 4.7 % as uncontrolled. Salbutamol was used as SABA inhaler therapy in all patients; concomitant ICS controller therapy was present in 55.8 % of patients. Interviews were performed in 14 patients (See Supplementary Material H). The following themes emerged (Fig. 3; Table 3).

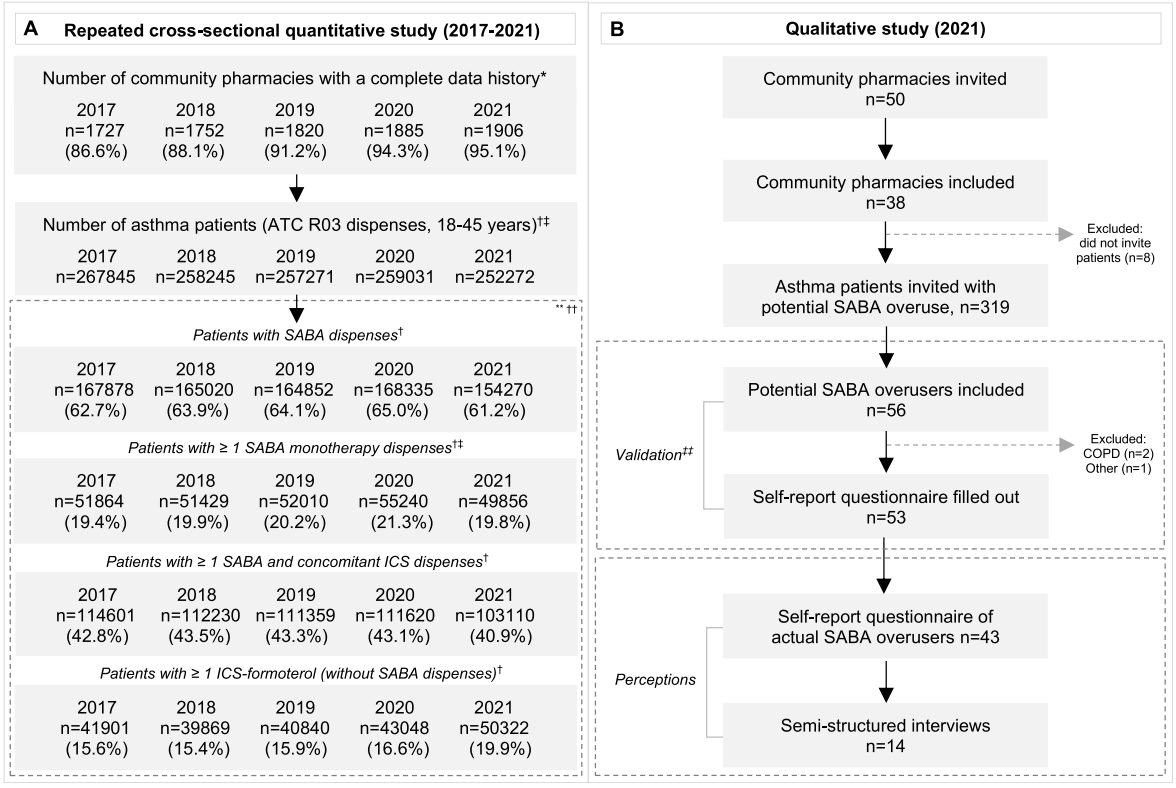

Fig. 1. Study flowchart of patient inclusion; (A) annually repeated cross-sectional quantitative study and (B) a qualitative study
*Community pharmacies with complete dispensing data for the appointed calendar year and the previous year were included.
†The number of patients was extrapolated to the total number of community pharmacies in the Netherlands within the corresponding calendar year (1994 in year 2017; 1989 in year 2018; 1996 in year 2019; 2000 in year 2020; 2005 in year 2021).
‡Starters with one SABA dispensing without any other ATC R03 dispensing indicated for asthma were excluded due to uncertainty in asthma diagnosis (76,210 in year 2017; 81,710 in year 2018; 83,229 in year 2019; 75,931 in year 2020; 76,238 in year 2021).
**Proportion of patients were calculated in relation to the defined study population of asthma patients per calendar year.
††Patients may be displayed in multiple subgroups according to the ATC R03 code dispenses.
‡‡The validation of SABA dispensing data as proxy measure for SABA overuse is shown in Supplementary Material G.
Abbreviations: ATC R03: Anatomical Therapeutic Chemical code for respiratory diseases; COPD: chronic obstructive pulmonary disease; ICS: inhalation corticosteroids; n: number of patients or community pharmacies; SABA: short-acting β_2-agonists.

3.2.1. Capability

3.2.1.1. Knowledge. A lack of knowledge on personal provoking triggers that set off or deteriorate asthma was reported in 79 % of patients. Trigger avoidance was perceived possible in 49 % of patients, mainly due to use of inhalers. Some triggers were considered unavoidable e.g. seasonal or exercise-induced causes. Other patients revealed an inadequate perception or denial of asthma as clinical indication due to its occasional symptom occurrence.

The mode of action of reliever and controller therapy was correctly distinguished in 77 % of patients. Likewise, use of SABA exclusively "as needed'' was acknowledged in 84 % of patients. Whereas, unawareness of the prophylactic effects of ICS therapy was sensed to cause SABA overuse in others.

3.2.1.2. Skills. SABA was administered as dry-powder inhaler (DPI) in 74.4 % and pressurized metered-dose inhaler (pMDI) in 25.6 % of patients for which the majority were unaware of at least one critical inhalation step with 72 % and 91 %, respectively (see Supplementary Material I). However, nearly all patients (86 %) articulated to have received sufficient information from HCPs to correctly use their inhaler (s) and some considered themselves an "expert''. Yet, 23 % of patients received an inhalation-instruction in the past year. Though, increasing awareness regarding their own abilities and the attainment of external feedback augmented others to reflect on and adjust their inhalation skills.

Use of pMDIs were considered more effective with the addition of a spacer, yet a burden due to its incompactness and lack of a dose counter as compared to DPIs. A greater objection was raised against frequent switching of inhaler devices due to different inhaler techniques. Device uniformity was present in 50 % of patients using both a SABA and ICS inhaler.

3.2.1.3. Memory, attention and decision process. Forgetting ICS controller therapy increased SABA use in 13 % of patients. One patient mentioned ICS intake had not yet formed a habit. However, structural ICS use was not considered burdensome in 96 % of patients. Some patients expressed intermittent ICS use as prevention only in circumstances when symptoms manifested, often in response to a cold or seasonal triggers. Whereas, some SABA monotherapy patients stated reluctance to "permanent'' ICS use.

In the past year, 47 % of patients visited HCPs for asthma care. Annual referral was however not perceived essential to optimal asthma management in 67 % of patients. Some described "no value-added'' or considered asthma monitoring their own responsibility, specifically in regard to (perceived) controlled asthma. Yet, an increased awareness on its relevance including their own involvement was evident when discussing their experiences, needs and wishes. Additionally, some patients expressed a desire for a more personalized and holistic approach including advice on lifestyle.

Table 1
Medication use in asthma patients with SABA overuse based on pharmacy dispensing data during a 5-year period (2017–2021).

Variables	Annual patients with SABA overuse[a]				
	2017	2018	2019	2020	2021
SABA overuse (>104 DDD/year), *n (%)*	53271	53088	53872	54836	51888
Proportion of all asthma patients	(19.9 %)	(20.6 %)	(20.9 %)	(21.2 %)	(20.6 %)
Proportion of all SABA users	(31.7 %)	(32.2 %)	(32.7 %)	(32.6 %)	(33.6 %)
SABA inhalation therapy					
SABA use (inhalations/day), *mean* ± *SD*[b]	0.99 ± 2.51	1.03 ± 2.67	1.05 ± 2.70	1.13 ± 12.7	1.09 ± 2.93
SABA use range, *n (%)*[‡]					
2–3 inhalations/week	27549 (51.7 %)	27636 (52.1 %)	27495 (51.0 %)	28139 (51.3 %)	26510 (51.1 %)
4–5 inhalations/week	12359 (23.2 %)	12203 (23.0 %)	12313 (22.9 %)	12591 (23.0 %)	11998 (23.1 %)
6–7 inhalations/week	5649 (10.6 %)	5485 (10.3 %)	5797 (10.8 %)	5876 (10.7 %)	5565 (10.7 %)
8–9 inhalations/week	2490 (4.7 %)	2429 (4.6 %)	2593 (4.8 %)	2656 (4.8 %)	2441 (4.7 %)
≥ 10 inhalations/week	5223 (9.8 %)	5335 (10.0 %)	5674 (10.5 %)	5575 (10.2 %)	5374 (10.4 %)
? Concomitant ICS inhalation therapy					
Concomitant ICS use, *n (%)*[b]	36730 (68.9 %)	36250 (68.3 %)	35870 (66.6 %)	36265 (66.1 %)	33744 (65.0 %)
Separate inhalers, *n (%)*[c]	15001 (40.8 %)	14617 (40.3 %)	14132 (39.4 %)	14062 (38.8 %)	12338 (36.6 %)
ICS (single)	13751 (37.4 %)	13402 (37.0 %)	13020 (36.3 %)	13005 (35.9 %)	11490 (34.1 %)
ICS and LABA	1003 (2.7 %)	989 (2.7 %)	882 (2.5 %)	833 (2.3 %)	663 (2.0 %)
ICS and LAMA	118 (0.3 %)	116 (0.3 %)	230 (0.6 %)	129 (0.4 %)	102 (0.3 %)
ICS, LABA and LAMA	128 (0.3 %)	110 (0.3 %)	110 (0.3 %)	94 (0.3 %)	83 (0.2 %)
Combination inhalers, *n (%)*[c]	21730 (59.2 %)	21634 (59.7 %)	21738 (60.6 %)	22204 (61.2 %)	21406 (63.4 %)
ICS/LABA	20290 (55.2 %)	20159 (55.6 %)	20388 (56.8 %)	20836 (57.5 %)	20173 (59.8 %)
ICS/LABA and LAMA (separate)	1440 (3.9 %)	1475 (4.1 %)	1350 (3.8 %)	1367 (3.8 %)	1221 (3.6 %)
ICS/LABA/LAMA	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (0.0 %)	12 (0.0 %)
ICS adherence (PDC), *mean* ± *SD*[c]	69.4 % ± 29.2 %	69.0 % ± 29.5 %	68.9 % ± 29.6 %	69.6 % ± 29.8 %	70.1 % ± 30.0 %
ICS adherence, *n (%)*[c]					
Adherent (≥80 % PDC)	16814 (45.8 %)	16513 (45.6 %)	16205 (45.2 %)	17089 (47.1 %)	16152 (47.9 %)
Non-adherent (<80 % PDC)	19916 (54.2 %)	19738 (54.4 %)	19665 (54.8 %)	19177 (52.9 %)	17593 (52.1 %)
Concomitant LABA without ICS inhalation therapy					
LABA without ICS use, *n (%)*[b]	328 (0.6 %)	299 (0.6 %)	334 (0.6 %)	344 (0.6 %)	341 (0.7 %)
Short-term OCS courses					
Short-term OCS courses, *n (%)*[b]					
≥1 course	8324 (15.6 %)	8644 (16.3 %)	8804 (16.3 %)	6655 (12.1 %)	6264 (12.1 %)
≥2 courses	2891 (5.4 %)	2960 (5.6 %)	2990 (5.5 %)	2286 (4.2 %)	2013 (3.9 %)
≥3 courses	1177 (2.2 %)	1183 (2.2 %)	1175 (2.2 %)	903 (1.6 %)	735 (1.4 %)

Abbreviations: DDD: daily defined dose; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonists; LAMA: long-acting muscarinic antagonists; n: number of patients; OCS: oral corticosteroids; PDC: proportion of days covered; SABA: short-acting β_2-agonists; SD: standard deviation.

[a] The number of patients was extrapolated to the total number of community pharmacies in the Netherlands within the corresponding calendar year (1774 relative to 1994 in year 2017; 1752 relative to 1989 in year 2018; 1820 relative to 1996 in year 2019; 1885 relative to 2000 in year 2020; 1906 relative to 2005 in year 2021).

[b] Descriptive statistics was performed on the defined population of patients identified with SABA overuse.

[c] Descriptive statistics was performed on the defined population of patients identified with SABA overuse and concomitant ICS use.

3.2.2. Motivation

3.2.2.1. Emotion. Anxiety for potentially occurring exacerbations led to SABA overuse in 14 % of patients, even if asthma symptoms were not present or intrusive. This was particularly encountered in patients with a negative asthma experience in the past. One patient mentioned a possible ‘‘psychological’’ dependence instead of a ‘‘medical’’ effect referring to encountered apprehensions when conscious of forgetting to inhale before exercising.

3.2.2.2. Beliefs about capabilities. The importance of SABA was acknowledged in 79 % of patients, primarily ascribed to a ‘‘symptom response’’ centered around its quick symptom resolution. Conversely, patients’ belief in ‘‘symptom prevention’’ was emphasized in 67 % of concomitant ICS users to attain and maintain improvement or symptom resolution, reducing SABA reliance. Some patients used SABA as ‘‘pre-caution’’ or ‘‘to open-up the lungs’’ before ICS intake. Whereas, other patients doubted the benefits of ICS due to the absence of direct perceivable effects.

3.2.2.3. Beliefs about consequences. The majority of patients (86 %) were unaware of the relative exacerbation risk when using SABA excessively. Moreover, necessitating SABA overuse was not considered an indication of poor asthma control in 51 % of patients. Some patients reported feeling an addiction for SABA use.

Apprehensions about potential side-effects of ICS controller therapy appeared to refrain its use in 24 % of patients. There was a sense that corticosteroids were regarded more harmful in relation to reliever therapy. However, side-effects were perceived in 4 % of concomitant ICS users.

3.2.3. Opportunity

3.2.3.1. Environmental context. Stockpiling of SABA inhalers at multiple locations in the surrounding area to ensure immediate relief when symptoms occur was reported in 48 % of patients or to avoid running out of medication in 39 % of patients. Early generated prescription refills were reported in 30 % of patients.

4. Discussion

This nationwide study has demonstrated the prevalence of SABA overuse among 20.6 % of asthma patients in the Netherlands, which remained constant from 2017 throughout 2021. Increased ICS-formoterol and decreased SABA inhaler dispenses were observed in starters of inhalation therapy in 2021, suggesting a possible onset of implementation of the 2019-updated GINA recommendations in reliever therapy. Notably, utilization of pharmacy dispensing data has shown to be an accurate and useful proxy measure for the identification of SABA overuse in asthma patients with a PPV of 81 %. Furthermore, this study conveyed new insights and extended existing understanding of key patient-drivers to SABA overuse in asthma; covering seven domains

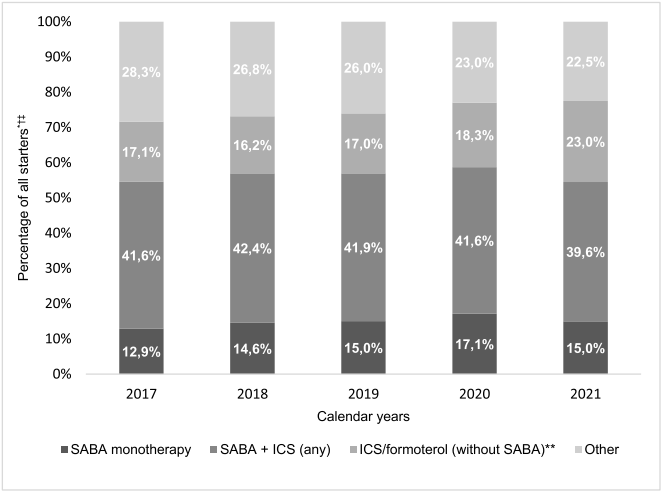

Fig. 2. Dispensing patterns of starters on asthma inhalation therapy during a five-year period (2017–2021).
*The number of patients was extrapolated to the total number of community pharmacies in the Netherlands within the corresponding calendar year (1774 relative to 1994 in year 2017; 1752 relative to 1989 in year 2018; 1820 relative to 1996 in year 2019; 1885 relative to 2000 in year 2020; 1906 relative to 2005 in year 2021).
†Patients with a first dispensing of the defined ATC R03 codes indicated for asthma are included (82,494 in year 2017, 79,946 in year 2018, 81,923 in year 2019, 75,410 in year 2020, 78,745 in year 2021).
‡Starters with one SABA dispensing without any other ATC R03 dispensing indicated for asthma were excluded due to uncertainty in asthma diagnosis (76,210 in year 2017; 81,710 in year 2018; 83,229 in year 2019; 75,931 in year 2020; 76,238 in year 2021).
**ICS with beclomethasone or budesonide (combination inhaler). The extent to which patients used their ICS-formoterol inhaler as reliever and/or controller therapy could not be identified.
Abbreviations: ATC R03: Anatomical Therapeutic Chemical code for respiratory diseases; ICS: inhalation corticosteroids; SABA: short-acting β_2-agonists.

based on an integrated theoretical framework related to capability, motivation and opportunity.

The present study revealed SABA overuse in over one-fifth of asthma patients in a real-world setting across the Netherlands. These findings are in line with previous (inter)national reporting, indicating suboptimal asthma management in a significant group of patients [37–41]. Despite the 2019-updated GINA strategy report recommendations, breaking the cycle of SABA overuse in asthma remains an ongoing challenge in clinical practice. This warrants reinforced attention from HCPs to actively identify patients in need of tailored behavioral interventions. A lack of grounding in theory and therefore inadequately targeted interventions towards individual determinants to SABA overuse may be causative for continuation of this medication-taking behavior in patients. Additionally, although the Dutch national guidelines have followed the recommended 2019-updated GINA report recommendations, SABA monotherapy is still recommended as step 1 in patients with minor and/or infrequent asthma symptom occurrence (<2 times/week during daytime). This is due to a lack of direct evidence supporting the pharmacotherapeutic value of incidental use of ICS as reliever therapy in these patients [26]. However, this discrepancy in reliever therapy strategy may be a strong barrier hampering implementation of the recommended paradigm shift in the Netherlands. Tackling this multifaceted complex SABA-taking behavior therefore requires a multidisciplinary approach, closely engaging relevant stakeholders from all healthcare-levels to maximize successful implementation of healthcare quality improvement. This warrants a systematic procedure of careful planning, delivering and continuous monitoring [3,42–44].

Valid measures of clinical medicine-taking behaviors are of utmost importance for HCPs to accurately perform periodical searches to identify suboptimal pharmacotherapy, optimize quality of care and ultimately improve clinical outcomes in patients [45]. To our knowledge, this is the first study to have proven the validity of pharmacy dispensing data as proxy measure for the identification of SABA overuse in asthma. The present study has demonstrated that when using this proxy measure 81 % of patients confirmed actual SABA overuse in daily practice. While many dispensing data approaches have been proposed in literature generating PPVs ranging from 37 to 100 %; the comparative interpretation of these results is limited by the use of various databases, target medications, populations, fixed look-back periods, golden standard metrics and clinical settings [46]. Moreover, utilization of dispensing databases are preferred over prescription databases, as it captures data on all redeemed medication [41].

This study highlights the broad range of attitudes, beliefs, preferences, fears and misconceptions regarding asthma and its pharmacological treatment perceived to influence SABA overuse in patients [23,24]. With the applied TDF and COM-B model as theoretical basis, 7 key

Table 2
Characteristics of study participants with confirmed SABA overuse (n = 43).

Characteristics	SABA overusers (n = 43)
Demographic characteristics	
Age in years, *mean ± SD*	48.5 ± 13.9
Age range, *n (%)*	
<46 years	16 (37.2 %)
46–65 years	23 (53.5 %)
>65 years	4 (9.3 %)
Sex (female), *n (%)*	26 (60.5 %)
Asthma related characteristics	
Clinical phenotype of asthma, *n (%)*[a]	
Allergic asthma	20 (46.5 %)
Non-allergic asthma	26 (60.5 %)
Exercise-induced asthma	17 (39.5 %)
Non-selective oral β-blocker	1 (1.9 %)
Unknown	1 (2.3 %%)
Duration of asthma	
<1 year	1 (2.3 %
1–10 years	8 (18.6 %)
>10 years	34 (79.1 %
SABA inhalation therapy	
SABA reliever therapy, *n (%)*	
Salbutamol	43 (100.0 %)
Terbutaline	0 (0.0 %)
SABA device, *n (%)*	
DPI	32 (74.4 %)
pMDI	11 (25.6 %)
Including use of a spacer	8 (18.6 %)
Breath actuated inhaler	3 (7.0 %)
Concomitant ICS inhalation therapy	
Number of patients with concomitant ICS, *n (%)*	24 (55.8 %)
ICS single inhaler, *n (%)*[b]	10 (41.7 %)
Combination inhaler (ICS/LABA), *n (%)*[b]	14 (58.3 %)
ICS device, *n (%)*[b]	
DPI	10 (41.7 %)
pMDI	14 (58.3 %)
Device uniformity for SABA and ICS, *n (%)*[b]	12 (50.0 %)
Asthma control indicators	
Current perceived asthma control, *n (%)*	
Well controlled	22 (51.2 %)
Partly controlled	18 (41.9 %)
Uncontrolled	2 (4.7 %)
Unknown	1 (2.3 %)
Number of short-term OCS courses, *n (%)*[c]	
≥1 course	10 (23.3 %)
Hospitalization due to asthma, *n (%)*[c]	0 (0.0 %)

Abbreviations: DPI: Dry Powder Inhaler; ICS: Inhaled Corticosteroids; LABA: long-acting β_2-agonists; OCS: oral corticosteroids; pMDI; pressurized Metered Dose Inhaler; n: number of patients; SABA: short-acting β_2-agonists; SD: Standard Deviation.
[a] Multiple options were possible.
[b] Descriptive statistics was performed on the defined population of patients with SABA overuse and concomitant ICS dispenses.
[c] In the prior 12-months based on patient answers.

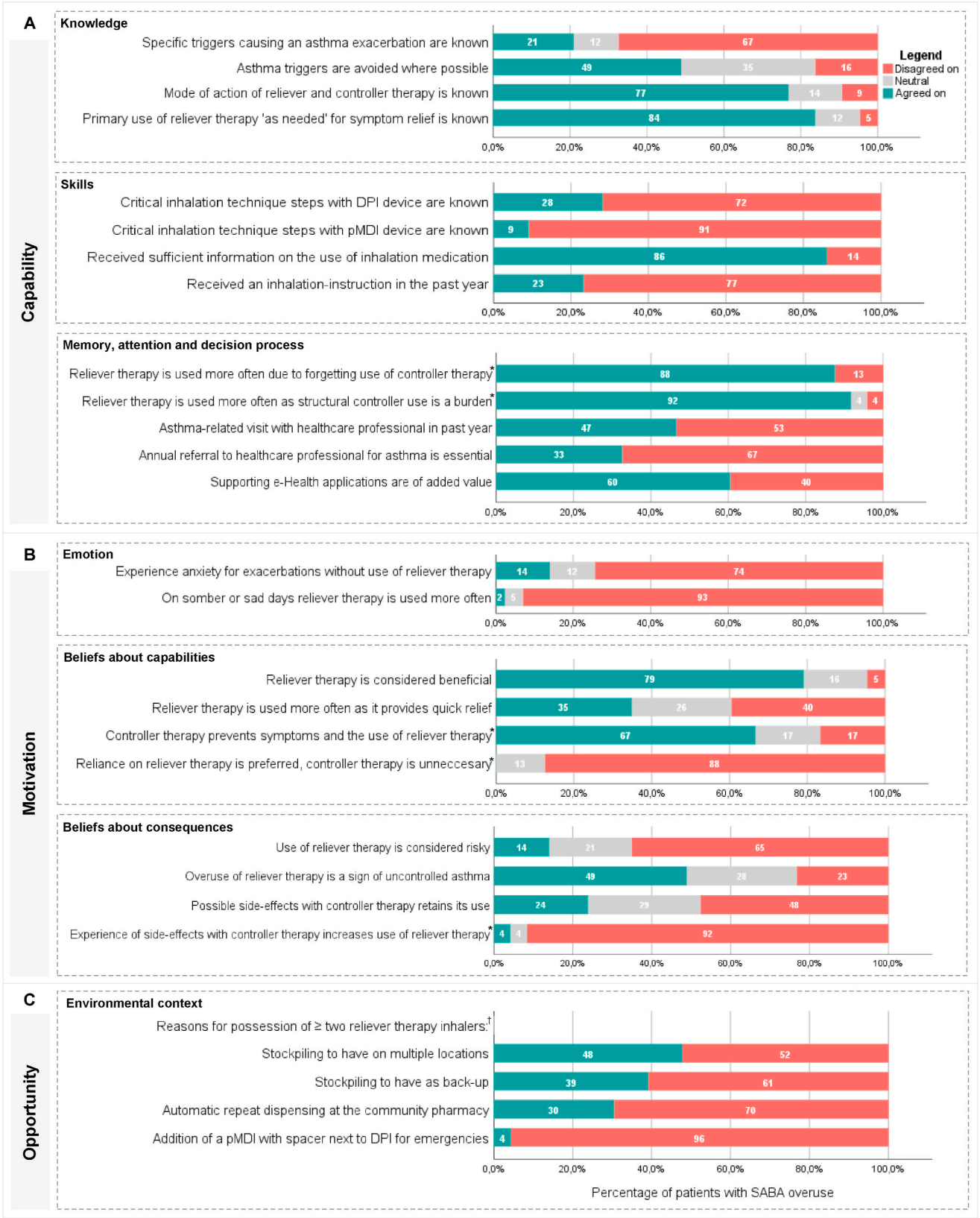

Fig. 3. Perceptions related to SABA overuse from the perspective of asthma patients (n = 43), divided into COM-B model constitutes and TDF-domains.
*Based on answers provided by patients with SABA and concomitant ICS therapy (n = 29).
†Based on an open-ended question; multiple reasons were mentioned in some patients (n = 23).
Abbreviations: COM-B; Capability Opportunity Motivation and Behavior; DPI: Dry Powder Inhaler; ICS: Inhalation Corticosteroids; n: number of patients; pMDI: pressurized Metered Dose Inhaler; SABA: short-acting β_2-agonists; TDF: Theoretical Domains Framework.

Table 3
Perceptions related to SABA overuse based on the perspective of asthma patients (n = 14), divided into COM-B model constitutes and TDF-domains.

TDF-domains	Themes	Illustrative quotes
Capability		
Knowledge	Knowledge on asthma triggers that set off or worsen asthma symptoms	*"It's just standard. I'm out of meds, I order new ones … I have no idea … why do I get shortness of breath? What have I done?.. I just want to know … why do I get this and how can I deal with it? Can I avoid it? So I can anticipate on it … or anticipate by adjusting your medication at that moment so I don't have to go to the doctor for another prednisolone course''* [P6]
	Unavoidable asthma triggers	*"I try my best in the hay fever season but it just doesn't work; It's really difficult in the summer … I also just want to exercise. I can of course stop exercising and it won't bother me but that's not really a solution. So you just carry on, I'm not going to stop exercising just to avoid taking it. I just have to carry my asthma medication with me and make sure that I always have it with me for when the need arises''* [P13]
	Knowledge on the clinical indication	*"I would call it an allergy and perhaps the feeling that I have bronchitis but it is characterized as asthma. Though, I wouldn't consider myself asthmatic. It may sound strange but I don't really feel like an asthma patient because it occurs occasionally''* [P8]
	Knowledge on the mode of action of inhaler therapies	*"Sometimes I doubt which one to inhale and then I take the Ventolin just to be sure … So that's a good question because I'm probably doing it wrong''* [P12]
Skills	Suboptimal inhaler technique	*"What I like about this inhaler is that you can actually taste the powder. So you feel that you are inhaling.''* [P4]
	Inhalation instruction and raising awareness on correct use	*"The explanation was a very long time ago but if you use it for a number of years you will become somewhat of an expert in your medication. It was never explained again or checked whether I was doing it correctly and then a few years later I was told but you have to do it this and that way''* [P62]*; "You are once again confronted with the facts: oh yes, this is how I should actually do it!''* [P6]
	Ease of use	*Well, I'm usually problem. I don't give myself time to inhale properly with the spacer [ICS] … I just want to do it fast … If I don't inhale properly, I notice after a week or so that it isn't going well. Then I still need the Ventolin. I notice when I inhale properly that the ICS does its job better''* [P6]*; I was supposed to use a spacer, but I never did. I always had it in my pocket so I could never take a spacer with me. I could only use it when I was home, but most of the time I use it outside. The redihaler is better for direct inhalation, so now I use this* one'' [P9]*; "You can also see how many doses there are left [DPI]; I really like that. You can't see that with an pMDI and at a given moment it runs out and then you have nothing''* [P4]
	Switching of inhalers	*"It's been crazy lately when it comes to changing brands of inhaler medication at the pharmacy, as it isn't reimbursed by the health insurance. You regularly get another, which I'm not happy with. With Tiotrus it took quite a long time before I felt that it did its job as I had to start over again; I think it's such a shame to adjust to the required force of inhalation again. I understand that everything costs money … it's not convenient''* [P10]
Memory, attention and decision process	(Un)conscious non-adherence ICS use	*"I have to put myself to it [ICS] in the evening. Then I think 'Oh, I still have to do that'. It's not in your system''* [P6]*; "If I forget to inhale it [ICS] for a day and go outside in the winter, I immediately feel shortness of breath and need the short-acting medication''* [P13]*; "After the first consultation, we didn't discuss the use anymore. He said use it permanently … I quickly noticed I don't always need it, so I started using it only when I had breathing problems''* [P5]*; "Then I have to use medication [ICS] permanently whilst I can receive help with this [SABA] occasionally. I'm not really open for this at the moment''* [P8]
	Shared treatment decision making (regular check-up)	*"It's not really discussed which inhaler types there are and which one suits me best … I trust the GP that he knows what he is prescribing me, but it is not wrong to be involved and to think about it together''* [P12]*; "I really wish it was monitored more and that I am asked more often how it is going and how I can improve certain aspects to further control my asthma. The little things I can do more''* [P13]*; "It seems important to do it every year so that you can evaluate how you are functioning at that moment and whether the medication and dose are still appropriate''* [P12]; *"I liked that about this research. It makes you think again; what do I actually want? You're in the rut of two puffs in the morning and evening and 'hey, I'll order again' … what do I want, which direction do I want to go?"*[P6]
	Healthcare provision (trust in HCPs and their set roles)	*"I believe the GP should encourage exercising regularly instead of puffing away all their lives … that's the most important, healthy living. Those corticosteroids do help, but … you can keep inhaling, but if you don't change your body and lifestyle, it'll only get worse''* [P9]; *"I have more of a connection with the GP. I find that more personal than with a pharmacist … so many people work there and you get a different person every time … I don't need that. I understand that it may be more convenient for the GP if it goes through the pharmacy to save time but I do like it more personal"*[P12]*; I already received all the information at a previous station. For me the pharmacy only involves the collection of my medication, it's more of a channel than information post for me''* [P7]; *"I think it's very good that the pharmacy pays close attention to the medication dispensed and intervenes when necessary''* [P4]
Motivation		
Emotion	Anxiety for exacerbations	*"I experienced reaching for it [SABA] too often … as soon as I got the idea that I might get short of breath, even if I didn't know yet, I immediately thought 'I just have to grab that blue disk' and then I can move on. It stems back from a bad experience. So, that's why I always want to have it with me so I don't end up in that situation again''* [P13]; *The preventive part before exercising may be more psychological than medical because I feel that I'm short of breath the moment I know that I forget my inhaler before exercising. Whilst if I had probably forgotten about it all together and thought about it after training … I don't know what would have happened.''* [P7]
Beliefs about capabilities	Quick symptom relief of SABA use	*"Very important [SABA] … I find it to be the most remarkable effective medication. Very positive about the effects because it works. You simply have immediate relief''* [P7]
	SABA use as precaution	*"I use it [SABA] in the morning because I wake up feeling a bit short of breath and in the evening it varies … sometimes as precaution and sometimes because I feel short of breath again''* [P12]; *"Sometimes I use Ventolin to open it up and 15 min later I inhale ICS … That's not the way to do it … but then I'm sure it will arrive [in the lungs] during a difficult time''* [P10]; *"I use it for sports and we are talking about heavy exertion sports … I exercise about five times a week''* [P7]
	Perceived necessity of ICS use	*"I cannot indicate whether the long-acting or slow-acting inhaler also has an effect … I especially notice that the short-acting inhaler has a good effect''* [P5]; *"A few weeks ago I found out that it was empty, the foster. It's probably been a few days now and I didn't feel short of breath or anything. I could also stop doing that … ''* [P9]; *"I needed it a lot less [SABA] after a few weeks, it [ICS] certainly had an effect. If I didn't have that, it would all be even worse now''* [P4]

(*continued on next page*)

Table 3 (*continued*)

TDF-domains	Themes	Illustrative quotes
Beliefs about consequences	Knowledge on risks of SABA overuse	*"With the short-acting drug I always thought it was reasonably safe, a fairly simple medicine in that sense. When I asked, it was only then that I was told: it is not very smart to use it excessively for a long time. I missed that information or needed it explained more clearly''* [P7]; *"I don't have the idea that it's harmful, at least short-term. Long-term I don't know. In that sense, I wonder* [P3]
	Addictive feeling	*"I didn't know that it could have an addictive feeling. At one point I experienced this myself because every time I needed it, when I felt shortness of breath which happened fast, I used my short-acting medication and it just got out of hand. At a certain point I became aware of that and it scared me* [P13]
Opportunity		
Environmental context	SABA on multiple locations; within reach	*"I do not only have it at home, also one in the car, one in my bag … I just want to have it with me everywhere I go so that when I need it, I have it within reach''* [P12]
	Early repeat prescription requests	*"I never wait until the last moment''* [P13]; *"It's never completely empty because I want to have some in stock''* [P12]
	Multiple SABA inhaler device types	*"I also have an inhaler with spacer, also Ventolin. The one with spacer for when I have a prednisolone course and I am really short of breath that I cannot inhale with the discus sufficiently … and I always have the discus in my bag for when I'm at work or in the evening when I'm feeling short of breath and still have the strength to inhale sufficiently''* [P6]

Abbreviations: COM-B; Capability Opportunity Motivation and Behavior; DPI: Dry Powder Inhaler; GP: General Practitioner; HCP: Healthcare Professional; ICS: Inhalation Corticosteroids; n: number of patients; P: patient number; pMDI: pressurized Metered Dose Inhaler; SABA: short-acting β_2-agonists; TDF: Theoretical Domains Framework.

domains emerged related to capability (*knowledge; skills; memory, attention and decision process*) motivation (*emotion; beliefs about capabilities and; consequences*) and opportunity (*environmental context)* [27–29]. Hence, this study represents the first critical step in the identification of individual key determinants to SABA overuse and the development of accompanying targeted interventions based on Behavior Change Techniques (BCTs). These techniques form the active ingredients and delivery procedures of complex interventions, designed to enhance effectiveness, replicability and implementation of existing interventions to guidelines [29,46,47]. The study of Visser et al., 2024 and Patton et al., 2018 have demonstrated potential for incorporating a theoretical basis in the identification and targeting of behavioral challenges regarding self-management of medication [48,49]. Moreover, incorporation of evidence- and theory-based interventions is endeavored by the Medical Research Council (MRC) for development and evaluation of complex interventions [50]. Future research will focus on interconnecting BCTs to identified key domains for specific evidence-based interventions, to provide a practical tool for use in clinical practice.

This study has a number of potential limitations. Utilization of pharmacy dispensing data provided by SFK lacked information on clinical diagnosis which may have influenced asthma disease validity. The quantitative study results may therefore not specifically resemble all asthma patients. However, to mitigate the risk of including COPD patients, an age restriction and selection of ATC R03 codes indicated for asthma were applied. This age group range has been determined a suitable proxy for asthma diagnosis [34]. Additionally, the healthcare setting and organization of care for asthma patients in the Netherlands might not be representative for other countries. In the Netherlands, patients usually visit the same community pharmacy repeatedly, facilitating the identification of suboptimal pharmacotherapy in patients on a pharmacy level [51]. Whereas, the utilization of national dispensing data might be a more suitable approach for patients visiting multiple pharmacies. Furthermore, an in-depth understanding of the underlying perceptions regarding SABA overuse was sought from a relatively small sample of voluntary asthma patients. Moreover, the asthma severity spectrum of patients could not be determined due to a lack of complete insight into their level of medication required to reach asthma control. Yet, patients across all asthma severities are at risk of severe or fatal exacerbations due to SABA overuse [3]. Nevertheless, selection bias was minimized by purposive sampling to ensure heterogeneity in characteristics and medication use.

In conclusion, the present findings demonstrate the continuous reality of SABA overuse in asthma across the Netherlands, despite the paradigm shift in reliever therapy. This reinforces the importance of a multidisciplinary approach, moving towards individualized healthcare support in asthma patients. Pharmacy dispensing data has proven to be valid for the identification of SABA overuse in asthma patients, facilitating HCPs to regularly monitor and actively select patients in need of tailored behavioral interventions. Potentially important patient-drivers to SABA overuse have been uncovered based upon a theoretical underpinning. The understandings gained are critical for the development of specific evidence-based behavioral interventions supported by BCTs, aimed at more effective self-management optimizing asthma control in clinical practice.

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Data availability statement

The data generated and analyzed supporting the conclusions of the qualitative study will be made available by the corresponding author on reasonable request, without undue reservation. Data supporting the findings from the population-based quantitative study were derived from SFK. Restrictions apply to the availability of these data, which were used under license for this study. The dataset is available from the corresponding author with permission from SFK.

CRediT authorship contribution statement

Claire D. Visser: Writing – original draft, Methodology, Investigation, Conceptualization. **Maaike R.A. Faay:** Writing – review & editing, Methodology, Investigation. **Ayşe Özdemir:** Writing – review & editing, Methodology, Investigation. **Henk-Jan Guchelaar:** Writing – review & editing, Methodology. **Martina Teichert:** Writing – review & editing, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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Appendix A. Supplementary data

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