NORWEGIAN SCHOOL
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Reported use of anti-asthmatic medication in doping control forms from 2015-2019

Mapping retrospective data

MA506 – Master thesis (30 ECTS)

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Abstract

Aim: Lower airway dysfunction (LAD) is common in athletes, especially in athletes engaged in sports with high ventilatory demands or exposures to irritants such as cold and dry air, polluted air and trichloramines. The mechanism for LAD among athletes is poorly understood; however, asthma plays an important role and two different phenotypes of asthma have been presented based on the presence of airway inflammation and respiratory symptoms. Treatment of LAD among athletes are the same as for asthma in the general population. We know that anti-asthmatic medication is among the most commonly reported pharmaceuticals among doping controlled athletes. Thus, the aim of this study was to further investigate the use of different anti-asthmatic products among doping controlled athletes.

Methods: This was an observational cross-sectional study, evaluating retrospective data from doping control forms (DCFs) obtained during 2015-2019 by Anti-doping Norway in recreational and elite athletes, some of whom reappearing with multiple forms.

Results: Of 10 418 DCFs, 1702 (16.3%) contained one or more anti-asthmatic products. Bronchodilators were the most frequently reported medications, with anticholinergics the most frequently among them. DCFs reported from females, national level athletes, and athletes with high risk of LAD contained significantly more anti-asthmatic products compared to their counterparts (p <0.01). Highest reported usage was seen among age-group 30-34 and among athletes from endurance sports.

Conclusion: Reappearance of the same athlete in the dataset is a weakness. However, the study provides data on how guidelines are adhered to and how asthma medications are used among athletes in Norway. We need more knowledge in this area.

Key words: Lower airway dysfunction, athletes, asthma treatment, asthma phenotypes, anti-doping

Total number of words (excluding front page, abstract, list of contents, list of abbreviation, tables, figures, references, and appendix): 11 186

Sammendrag

Hensikt: Astma og respiratoriske plager er vanlig blant idrettsutøvere, spesielt blant idrettsutøvere med høye ventilasjonskrav og som foregår i et ugunstig klima som kald og tørr luft, forurensning og trikloraminer. Mekanismene for astma blant idrettsutøvere er lite forstått, men to ulike fenotyper har blitt presentert basert på tilstedeværelse av allergi, luftveisinflammasjon og respiratoriske symptomer. Behandlingen av astma blant idrettsutøvere er imidlertid den samme som for den vanlige befolkningen. Det er vist at anti-astmatiske medisiner var blant de hyppigst rapporterte farmasøytiske produkter blant dopingkontrollerte utøvere. Hensikten med denne studien er å videre undersøke den rapporterte bruken av ulike astmamedisiner blant doping kontrollerte idrettsutøvere.

Metode: Dette var en tverrsnittstudie ved å kartlegge retrospektive data fra dopingkontrollskjemaer gjennomført i løpet av 2015-2019 av Anti-doping Norge. Både topp- og breddeutøvere er inkludert, hvor noen representerer flere skjemaer.

Resultat: Av 10 418 dopingkontrollskjemaer, inneholdt 1702 (16.3%) inneholdt et eller flere anti-astmatiske produkter. Bronkodilaterende medisiner var de mest rapporterte anti-astmatiske medisinene, hvor antikolinergika var mest rapportert av disse. Dopingkontrollskjemaer fra kvinner, utøvere på nasjonalt nivå og utøvere med høy risiko for astma inneholdt signifikant mer anti-astmatiske produkter sammenlignet med menn, idrettsutøvere på breddenivå og idrettsutøvere med lav risiko for astma (p <0.01). Høyest rapportert bruk ble sett blant aldersgruppen 30-34 år og blant utøvere fra utholdenhetsidrett

Konklusjon: Gjengangere av samme idrettsutøvere i datasettet er en svakhet. Selv om denne studien gir innsikt i hvordan retningslinjer følges og hvordan astmamedisin brukes blant idrettsutøvere i Norge, trenger vi mer kunnskap på dette området.

Nøkkelord: Nedre luftveisplager, idrettsutøvere, astmabehandling, astma fenotyper, anti-doping

Totalt antall ord (ekskludert forside, sammendrag, innholdsfortegnelse, forkortelsesliste, tabeller, figurer, litteraturliste og vedlegg): 11 186

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Preface

Firstly, I am beyond grateful for all the experiences and knowledge I have gained throughout five years of studies by the Norwegian School of Sports Science. Writing the master thesis was an enjoyable process until my father was diagnosed with cancer at the beginning of March. Since then, it has served as an escape from the reality and a confidence booster. I am therefore incredibly proud of myself and the final result, with essential support from my supervisors, family, friends, and others.

The biggest thank you to my supervisor, Trine Stensrud. You have not only been the greatest support and motivator on both the bachelor- and master thesis, but also have given me the opportunity to learn incredibly much the past years. As cliché as it sounds; *I would not have been me if it weren´t for you.*

A big thank you to Thomas Halvorsen. Your feedback and support have been essential during this process. I really appreciate all our discussions and conversations throughout this period and am beyond grateful for having you as my co-supervisor.

Also, a big thanks to my co-supervisor at Anti-Doping Norway, Astrid Gjelstad, for patiently making me understand both the data set and the code language used in the anti-doping and pharmacy world.

Dear pappa and little brother August, thank you for being my biggest supporters no matter what. You will now have my full attention and we will continue to fight this war.

Dear mamma, I miss you every day and hope you are proud of me, August and pappa. I hope and believe that some of the qualities I inherited from you have been essential writing this thesis.

And lastly, thank you to my boyfriend Stian, for being the smartest and most humble person I know. Supporting me this spring and at the same time finishing your own thesis cannot have been easy for you. I´m lucky to have you and your family.

Aurora Jørnsdatter Kojen - Rissa, May 2024

List of abbreviation

BHR/AHR	Bronchial hyperresponsiveness/Airway hyperresponsiveness
BPT	Bronchial provocation test
DCF	Doping Control Forms
EIA	Exercise-induced asthma
EIB	Exercise-induced bronchoconstriction
FeNO	Fractional exhaled nitric oxide
FEV1	Forced expiratory volume in one second
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
ISTI	International Standard for Testing and Investigation
LABA	Long acting β2-agonists
LAD	Lower airway dysfunction
LTRA	Leukotriene receptor antagonists
RTP	Registered Testing Pool
SABA	Short acting β2-agonists
TUE	Therapeutic Use Exemption
WADA	World Anti-Doping Agency

1. Thesis structure

This master's thesis consists of an extended theory and method chapter followed by a research article, in accordance with the requirements for the master's thesis in the subject MA506 – Master thesis (30 ECTS). The theory chapter consists of an extended description of the current knowledge and statement of the problem area. Further, the extended methodology consists of an expanded description of the data handling of the data set received from Anti-Doping Norway (ADNO). The research article is developed following the guidelines for research articles by BMJ Open, and the structure of the article follows the STROBE Checklist: cohort, case-control, and cross-sectional studies (combined) (BMJ Open, w.y.; Strengthening the reporting of observational studies in epidemiology, 2024).

1.1 Notes about thesis

In this thesis, artificial intelligence (AI) is used as a tool for spelling/formulation and to create formulas in Excel. See appendix 1 and 2 for examples. Both ChatGPT 3.5 (https://chat.openai.com/) and SIKT (https://ki-chat.sikt.no) were used. Before AI chatbots were used for this thesis, the undersigned familiarized themselves with information about safe use of AI from the library at the Norwegian School of Sport Sciences (Torset, 2023). AI is **NOT** used to produce entire text or to search for information or references on the topic.

2. Theory

2.1 Defining asthma

Global Initiative for Asthma (GINA) defines asthma as" a *heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation."* (GINA, 2023, p. 22). In terms of lung physiology, asthma is typically characterized by reversible airflow obstruction, bronchial hyperresponsiveness (BHR) and distinct patterns of airway inflammation (GINA, 2023, p. 22). Definitions of asthma are generally consensus-based, recognizing a disease heterogeneity with clusters of demographics, clinical and/or pathophysiological characteristics often called "asthma phenotypes" (Kuruvilla et al., 2019).

BHR can be described as an increased sensitivity to different factors that conduce to excessive airway narrowing, also called bronchoconstriction (Carlsen et al., 2008a, p. 388; Sterk & Bel, 1989). Typical triggering factors to bronchoconstriction in individuals with BHR are cold, exercise-related hyperpnea, or irritants such as chlorine and pollution (Carlsen et al., 2008a, p. 392; Helenius et al., 1997, p. 160; Helenius et al., 1998). BHR is present in the majority of individuals with asthma. However, the presence of BHR alone does not confirm an asthma diagnosis, as the phenomenon may be seen also in other respiratory disorders, such as premature birth and patients with cystic fibrosis, as well as in healthy subjects (Cockcroft, 2010, pp. 18-19; Kotecha et al., 2018; McCuaig & Martin, 2013). In athletes, there is a notable increase in the prevalence of BHR, although with distinct differences between different sports, typically most pronounced in endurance athletes and linked to intense training over extended periods (Bernhardsen et al., 2022; Brannan & Porsbjerg, 2018). In real life, BHR often reveals itself as bronchoconstriction after vigorous exercise, a scenario labeled exercise-induced bronchoconstriction (EIB). EIB has been defined as a term used to describe airway narrowing to exercise in both those with clinical symptoms of asthma (in the past labelled "exercise-induced asthma") and those who experience EIB in the absence of clinical asthma (Anderson & Kippelen, 2005, p. 116; Carlsen et al., 2008a, p. 388; O'Byrne & Inman, 2003). EIB is often seen as an indicator of active and treatable pathophysiology in persons with asthma. EIB is defined as 10 % or more reduction in forced expiratory volume in one second (FEV_1) after a standardized exercise test (Carlsen et al., 2008a, p. 389).

The mechanism of EIB in athletes are not fully understood. However, three different theories are proposed: *The osmotic theory, the thermal theory and the recurrent epithelial microtrauma theory"* (Couto et al., 2018; Rasmussen, Hansen, & Backer, 2022, p. 02). *The osmotic theory* suggests that dehydration of the airway occur as a consequence of increased ventilation. The dehydration causes a hyperosmotic state in the airway mucosa which is associated with release of inflammatory mediators and further contraction of the bronchial smooth muscle (Ali et al., 2012, p. 481). *The thermal theory* proposes that increased ventilation leads to dehydration in the airway wall because of changes in temperature, which lead to local vasoconstriction. Upon the restoration of normal temperature, blood vessels become hyperpermeable, causing distension, bronchial wall edema, and subsequent bronchoconstriction (Couto et al., 2018, p. 10). *The recurrent microtrauma* suggests that increased ventilation can be seen as a stress-factor on the airway, leading to injury in the airway epithelium, such as plasma exudation and microvascular leak. This recurring cycle of injury and repair induces changes in the contractile properties of airway smooth muscle, following exposure to plasma-derived products, thereby contributing to the development and progression of airway hyperresponsiveness in athletes (Kippelen & Anderson, 2012, p. 387; Kippelen et al., 2018).

Studies suggest that increased parasympathetic activity may be linked to asthma and BHR in athletes, indicating a role in the pathogenesis (Knöpfli & Bar-Or, 1999). Studies that measure parasympathetic activity in athletes aid our efforts to understand asthma development in athletes. The type of sport has been shown to influence BHR severity and its relationship to parasympathetic activity (Kaltsatou et al., 2011, p. 2085) Thus, the association between BHR and parasympathetic activity seems stronger in swimmers, and cardiac vagal activity seems more closely related to BHR than pupillometry (Pichon et al., 2005, p. 27; Stang et al., 2016, pp. 2104-2105). Parasympathetic activity in EIB is associated with a bronchodilating effect of ipratropium bromide (anticholinergics), indicating a beneficial effect from blocking cholinergic pathways in their airways (Stang et al., 2016, p. 2106) These are intriguing findings that support the use of this class of medication in athletes with EIB.

Airway inflammation in asthma involves pathological changes in the airway epithelium and submucosa, consequently leading to airway remodeling in the long term without optimal treatment (Fahy, 2015, p. 60; Locksley, 2010, p. 778). This inflammation predisposes individuals to asthma exacerbations by narrowing airway caliber and exaggerating responses to inhaled triggers. The severity of asthma can vary greatly between patients, with phenotypic clusters showing differences in airflow obstruction and susceptibility to exacerbations (Locksley, 2010, pp. 779-780). Understanding the underlying cellular and molecular mechanisms of airway inflammation is crucial for personalized treatments (Fahy, 2015, p. 61).

2.2 Pheno- and endotypes of asthma in athletes

Because of its heterogeneity, asthma is usually split into different clusters or endotypes. While the precise classification of asthma endotypes remains incomplete, it is currently broadly categorized into type 2 asthma and non-type 2 asthma based on the immunological findings (Fahy, 2015, p. 57). Type 2 inflammation in asthma is characterized by the secretion of cytokines IL-4, IL-5, and IL-13 by Th2-cells, leading to increased IgE and eosinophilia. It is associated with allergic rhinitis and increased fractional exhaled nitric oxide (FeNO), mainly mediated by eosinophils, mast cells basophils, Th2 cells, ILC2s, and IgE-producing B cells (Fahy, 2015, p. 59; Rasmussen, Hansen, & Backer, 2022, p. 04). This type of asthma is seen as the classical early-onset asthma.

Th2-low or non-Th2 asthma refers to asthma cases with low levels of type 2 inflammation in the airways, comparable to the normal range seen in healthy individuals. This type of inflammation is not fully understood but is often referred to as the late-onset asthma and is more prevalent among women, obese individuals, and smokers (Dunn et al., 2018, p. 285; Sze et al., 2020, p. 312). Patients with Th2-low asthma may have a mix of multiple disease endotypes affecting small subgroups, possibly involving intrinsic airway abnormalities or other factors like oxidative stress, IL-17, or neutrophil products driving airway hyperresponsiveness and obstruction (Bougault et al., 2009, pp. 743-745) Despite differences, both asthma endotypes involve mast cells, which play a pivotal role in airway inflammation (Altman et al., 2019, p. 4986; Hallstrand et al., 2013, p. 4)

Rasmussen and colleagues investigated the presence of Th2- and non-Th2 inflammatory patterns among elite Olympic athletes (2022, p. 2250). Among the 1375 athletes included, 16.5% were found to have asthma by a previous doctor's diagnosis or a positive bronchial hyperresponsiveness test, with highest prevalence among endurance athletes. Based on presence of inflammatory markers, 69.8% of the asthmatic athletes were classified as Th2-asthma and 30.4% as non-Th2 asthma. The findings also indicate that athletes with non-Th2 asthma experienced fewer allergy symptoms and were less likely to have doctor-diagnosed allergic rhinitis. This suggests that non-Th2 asthma may develop in elite athletes after several years of intensive training. It has been suggested that asthma in endurance athletes could be a result of prolonged mechanical stress on the airway surface and increased ventilation leading to airway remodeling (Rasmussen, Hansen, Stensrud, et al., 2022, p. 2251).

Couto and colleagues have also investigated the presence of inflammation among asthmatic athletes, dividing them into "atopic asthma" and "sports asthma" (2015). Athletes with "atopic asthma" were characterized by the typical biomarkers seen in Th2-asthma (Couto et al., 2015, p. 900). On the other hand, athletes with "sports asthma" were characterized with absence of the typical biomarkers associated with Th2-asthma, and nevertheless increased respiratory symptoms and BHR during exercise (Couto et al., 2015, p. 901). Respiratory symptoms in sports asthma were particularly prominent during high-intensity exercise in environments with irritants such as chlorine products, pollution, or cold air. Out of the 150 asthmatic athletes 69.3% were classified as atopic asthma, while 30.7% had sports asthma (Couto et al., 2015, p. 901).

Tsukioka and his team in Japan studied how symptoms vary among elite athletes between what they labelled as classic asthma and sports asthma, discovering a similar distribution but with two additional distributions of sports asthma (Tsukioka et al., 2017, p. 554). Thus, the authors suggested three clusters of asthma in these Japanese athletes, with differences in characteristics such as symptom, atopic features, %FEV_1-values, and response to inhaled corticosteroids (ICS) treatment. Cluster 1 athletes had a less atopic phenotype with normal lung function. Cluster 2 athletes also had less atopic phenotype but lower %FEV_1-values despite fewer symptoms. Cluster 3 athletes exhibited a strong atopic phenotype with high eosinophil count, total IgE levels, and increased airway response to methacholine, resembling Th2-asthma. After treatment with ICS, cluster 2 athletes showed improved %FEV_1-values, while cluster 3 athletes had a significant decrease in FeNO values compared to pretreatment values. These differences suggest heterogeneous asthma phenotypes among athletes but need to be further investigated (Rasmussen, Hansen, & Backer, 2022, p. 06; Tsukioka et al., 2017, p. 555).

As a collective term for asthma-related issues in athletes, lower airway dysfunction (LAD), is presented (Hull et al., 2021, p. 6; Schwellnus et al., 2022, p. 1090). This is an umbrella term that includes exercise-induced asthma (EIA), exercise-induced bronchoconstriction (EIB) and bronchial hyperresponsiveness (BHR) with lack of classic inflammatory features (Reier-Nilsen, Sewry, et al., 2023, p. 481). The term will be used to describe all the conditions mentioned above unless otherwise specified.

2.3 Lower airway dysfunction in athletes

The most recent comprehensive examination of LAD prevalence in athletes has been presented in a systematic review and meta-analysis by Price and Colleagues (2022). This comprehensive article incorporated data from 67 diverse studies, reliving an overall prevalence rate of 21.8% over the past three decades (since 1990) . The most common subtypes of LAD among athletes were airway hyperresponsiveness (AHR) (38.2%), EIB (21.0%) and asthma (17.8%) respectively (2022, p. 215) Sex-based comparisons within the included studies indicate a significantly higher prevalence of AHR among females (15.5%) compared to males (11.5%) (2022, p. 216) The highest prevalence of LAD was found in aquatic (39.9%), winter (29.5%), and endurance sports (25.1%). This can be explained by risk factors such as cold and/or polluted air, and chlorine products (2022, p. 216) However, the diagnostic approach seems to play a pivotal role in prevalence disparities, with direct bronchial provocation tests (BPTs) revealing the highest prevalence compared to alternative diagnostic approaches such as indirect BPTs and reporting symptoms Price et al. (2022, p. 217) The difference in diagnostic approach may explain the difference in prevalence in different studies.

2.4 Diagnostic approach to lower airway dysfunction

GINA have proposed diagnostic algorithms for asthma according to age-groups (2023, p. 25). A potential diagnosis of asthma among adults is examined in the light of (1) self-reported symptoms and features and (2) standardized laboratory tests confirming potential expiratory airflow limitations (GINA, 2023, p. 25). Typical self-reported symptoms can be wheezing, chest tightness, coughing and shortness of breath. It is also important to detect typical triggers for the symptoms and if there is a family history for asthma (GINA, 2023, p. 25).

The laboratory test used to detect variable airflow limitation is typically the bronchodilator responsiveness test, i.e. testing if a bronchoconstriction is present which is responsive (or reversible) to a bronchodilator. This test is often called a reversibility test, and usually consists of performing a spirometry before and after providing 200-400 µg salbutamol or equivalent. A significant improvement in lung function is characterized by an increase in FEV_1 of 12% or more and >200mL (GINA, 2023, p. 25; Miller et al., 2005, p. 327). If parasympathetic activity is suspected to play a role in the patients´ symptoms, anticholinergics can be used as bronchodilator (Carlsen et al., 2008b, p. 496).

In line with the pivotal role played by BHR in asthma, bronchial provocations tests (BPT) are often used (GINA, 2023, p. 27). The main purpose of a BPT is to test airway sensitivity to stimuli expected to cause bronchoconstriction, using either direct or indirect irritants. A direct BPT involves inhalation of chemical agents (eg. Methacholine or histamine) which directly stimulate the smooth bronchial muscle to provoke bronchoconstriction (Coates et al., 2017, p. 3). The purpose of an indirect BPT is to mimic the processes that promotes bronchoconstriction under conditions characterized by hyperpnea, such as in EIB (Hallstrand et al., 2018, pp. 3-4). This includes methods like eucapnic voluntary hyperpnea (EVH) and EIB-test. The EVH test aims to mimic the hyperosmotic trigger of EIB through high-volume ventilation for 6 minutes while inhaling a specific air mixture of 21% oxygen, 5% carbon dioxide, balanced by nitrogen. An EIB-test requires the patient to perform high-intensive exercise over a short period of time (6-8 min) without warm-up. The purpose is to imitate the same mechanisms that occur during ordinary training (Hallstrand et al., 2018).

Given the ongoing uncertainty surrounding the prevalence of asthma phenotypes among athletes, numerous studies have aimed to compare different diagnostic tools to improve the diagnostic accuracy. Although there is no established gold-standard, researcher have tried to investigate specificity and sensitivity in different diagnostic tests (Reier-Nilsen, Sewry, et al., 2023; Reier-Nilsen, Stang, et al., 2023). In the systematic review and meta-analysis by Reier-Nilsen and colleagues, the focus was on comparing the performance of various diagnostic BPTs in assessing LAD in athletes, with the aim of informing optimal clinical practice (2023). The researcher suggests that indirect BPTs, such as EIB-test and EVH, demonstrated moderate specificity. Notably, a field-based, sport-specific EIB-test was found to be more specific than both laboratory-based EIB-test and EVH while direct BPTs showed lower overall sensitivity in detecting LAD among athletes (Reier-Nilsen, Sewry, et al., 2023, p. 8). In a recently published study by Reier-Nilsen and colleagues, it was found that unsupervised field-based EIB-test may also detect LAD among athletes (Reier-Nilsen, Stang, et al., 2023, p. 9). Given the absence of a gold-standard test, these findings are challenging to evaluate. Therefore, caution must be considered in the interpretation and the application of these results. Further research is clearly needed in this complex and evolving landscape.

2.5 Treatment and prevention of lower airway dysfunction

The treatment for LAD can be classified as self-management and management with medications (GINA, 2023, p. 49). For athletes, self-management needs to be considered regarding the exposure of different irritants that can provoke symptoms (Carlsen et al., 2008b, p. 493) For example, for winter athletes, such as cross-country skiers, it may be necessary to reduce exercise intensity, and try to avoid high-volume ventilation in cold air. Further, athletes with a Th2-type asthma and allergies to pollens should take precautions during the pollen season. However, the practicality of such precautions needs careful considerations. For example, swimmers rely on swimming pool workouts for exercise effectiveness, making it challenging to avoid chlorinated environments which may harm their airways. Future research should explore environmental modifications that could reduce respiratory symptoms and lung injuries among athletes, for example improved ventilation systems in swimming halls.

In addition to personal efforts aiming to control symptoms, pharmaceutical interventions play a crucial role in managing LAD in athletes (GINA, 2023, p. 49). In general, pharmaceuticals are generally categorized into two main types: reliever medications and controller medications (Carlsen et al., 2008b, pp. 493-495; GINA, 2023, p. 55). The purpose of the controller medications is to reduce airway inflammation, control symptoms and reduce further deterioration in lung function.

Controller medications are typically inhaled corticosteroids (ICS) and /or leukotriene receptor antagonists (LTRA), and they are used as a long-term treatment (GINA, 2023, p. 55). Reliever medications are typically used as short-term reliever treatment after symptoms have become apparent, or used as short-term preventers before the individual is entering into a situation known to be a trigger to symptoms, such as exercise. Much used relievers are short acting β2-agonists (SABA) and anticholinergics (GINA, 2023, p. 56). These medications were previously also administered orally, but inhalation is by far the most common route. Following, the typical medicines related to LAD-management will be described.

2.6 Reliever treatment

2.6.1 β2-agonists

Inhaled β2-agonists serve as potent bronchodilators in managing symptoms associated with LAD (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023a). These medications are classified into short-acting β2-agonists (SABA) and long-acting β2-agonists (LABA). The most commonly used SABA's are salbutamol and terbutaline. These substances bind to the β2 receptors on the smooth muscles of the bronchioles, leading to acute bronchodilation if bronchoconstriction is present, with the effect becoming evident after a few minutes and lasting for 4-6 hours (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023a).

LABA´s are commonly represented by medications such as salmeterol and formoterol (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023b). Like SABA´s, LABA´s also target the β2 receptors on the smooth muscle cells lining the bronchioles. However, they exhibit a slower onset of action, thereby extending bronchodilation for up to 12 hours post-administration. Variations exist among these agents; and importantly, formoterol demonstrates a more acute bronchodilator effect compared to salmeterol which exhibits a slower onset of effect (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023b). Moreover, vilanterol serves as an ultra-long-acting β2-agonist, often utilized in combination with ICS for enhanced long-term efficacy (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023f)

2.6.2 Anticholinergics

The release of acetylcholine, which binds to muscarinic receptors, triggers an increase in Ca^{2+} within the cells, leading to bronchoconstriction. Anticholinergics work by blocking muscarinic receptors in the airways, thus preventing acetylcholine from binding and initiating bronchoconstriction (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023e). This class of medication is particularly effective for vagus-induced bronchoconstriction. Ipratropium bromide is as short-acting anticholinergic (short acting muscarine antagonist), often abbreviated SAMA, that begins to take effect within minutes and provides relief for 4-6 hours. In contrast, tiotropium bromide is a long-acting anticholinergic (long acting muscarine antagonist or LAMA) that starts working after 30 minutes. It is worth noting that maximal bronchodilation efficacy typically occurs after three days of continuous treatment (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023e).

2.7 Controller treatment

2.7.1 Inhaled corticosteroids

Inhaled corticosteroids (ICS) are potent glucocorticoids characterized by their localized action within the bronchial tree. This targeted approach minimizes systemic effects while delivering a pronounced local anti-inflammatory effect in the bronchial mucosa primarily mediated through cytokine modulation (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023c). This mechanism reduces the influx of neutrophil granulocytes, consequently reducing airway inflammation. Additionally, ICS have demonstrated efficacy in reducing vessel permeability, improving bronchial secretion viscosity, and enhancing adrenergic β2-receptor formation. These effects diminish airway reactivity, thereby mitigating airflow obstruction, improves symptoms and reducing the necessity for oral glucocorticoids. While available preparations generally offer comparable effectiveness at equipotent doses, individual responses may vary (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023c).

2.7.2 Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRA) are a class of oral anti-asthmatic medications characterized by a dual action involving anti-inflammatory and bronchodilator effects. The most commonly LTRA´s are Montelukast. The effectiveness in asthma has been shown to vary between individuals. LTRA works by blocking cysteinyl leukotriene-1 receptors, which are involved in bronchial constriction and allergic responses. As a result, it prevents bronchial constriction while also reducing the inflammatory response associated with leukotrienes. The mechanism also reduces the recruitment of eosinophilic leukocytes to the bloodstream, sputum, and bronchial wall (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023d).

LTRA offers a notable protection against lung function deterioration triggered by exertion, allergens, and exposure to cold air. In addition, they quickly improve allergic rhinitis, a benefit considerable significance for numerous asthmatic individuals. LTRA´s distinct mechanism of action in addressing inflammation in asthma, separate from ICS, suggests a potential additive effect when used in conjunction with these medications (Legemiddelhåndboka [Handbook of pharmaceuticals], 2023d).

2.8 What is the gold-standard treatment for athletes?

As discussed previously, asthma medication can be categorized as reliever and controller medication. Based on these categories, combination therapies have been developed, often by using a single device to administer different classes of medication, tailored to meet individual goals. Maintenance-and-reliever therapy (MART) consists of a long-term treatment regimen and includes both LABA and ICS to be used systematically over time. Anti-inflammatory reliever (AIR) therapy consists of low-dose ICS and a rapid-acting bronchodilator, to be used as needed (GINA, 2023, p. 56) Further, GINA guidelines advise a stepwise approach based on disease severity, describing a preferred and an alternative escalation route (GINA, 2023, p. 58). For adolescents and adults, the preferred model recommends starting with the AIR-strategy, using low-dose ICS-formoterol when needed (mild asthma, step 1-2) (GINA, 2023, p. 58). If ineffective it is recommended to continue with step 3-5 suggesting the MART-strategy, with low to high dose maintenance ICS-formoterol (moderate to severe asthma). The alternative escalation route suggests using ICS whenever taking SABA as a reliever (step 1-2, AIR-strategy), and further low to high dose maintenance ICS-LABA/LAMA as step 3-4 (MART-strategy) (GINA, 2023, p. 65). The choice of strategy needs to be considered based on the severity and the endotypes.

As per GINA guidelines, it is cautioned against using β2-agonists as monotherapy due to the potential risk of developing resistance as well as masking airway inflammation potentially giving rise to severe attacks (Kaplan et al., 2020, pp. 5-6). Consequently, the recommendation is to employ LABA in combination with ICS as maintenance treatment (GINA, 2023, p. 56), and more lately, also advising against the use of SABA without ICS.

For athletes diagnosed with EIB, it is important to manage the underlying LAD effectively to ensure they can compete on an equal footing with athletes without these conditions (Allen et al., 2019, p. 663; Rasmussen, Hansen, & Backer, 2022, p. 5). The recommendation for managing LAD in athletes is currently the same as for the general population, i.e., basically inhaled corticoids combined with a bronchodilating agent (GINA, 2023, p. 65; Rasmussen, Hansen, & Backer, 2022, p. 5). For athletes experiencing EIB symptoms, it is now proposed to use SABA pre-exercise together with low-dose ICS, similarly to what is also recommended in non-athletes (GINA, 2023, p. 65; Rasmussen, Hansen, & Backer, 2022, p. 5). SABA is usually highly effective against symptoms associated with EIB, and in previous versions of GINA guidelines it was recommended to use SABA alone. As EIB is currently understood within an inflammatory paradigm, the current version of GINA recommends using SABA in combination with ICS (GINA, 2023).

2.9 Are anti-asthmatic products performance-enhancing?

Given the physiological effects of asthma medications, one might consider the possibility that reversing symptoms could enhance performance beyond merely restoring normal physiological function, potentially classifying such treatment as doping. Supporting this perspective, it has been shown that athletes with a documented history of asthma have outperformed their non-asthmatic counterparts in Olympic Games competitions (Fitch, 2012, p. 415).

The public debate over the use of anti-asthmatic products became particularly prominent following the hacking of WADA by the Russian hacker group *Fancybear*, when the Therapeutic Use Exemption-list (TUE) regarding the use of anti-asthmatic medication among prominent athletes were leaked (World Anti Doping Agency, 2016). The discussion mainly revolved around public perceptions suggesting that anti-asthmatics enhance performance, and the opinions of some athletes who argued against the participation of individuals using such medication in sports (Smith, 2016). The discussion, which received extensive media coverage, resulted in a stigma surrounding the use of these medications, leading athletes to report avoidance of prescription drugs (Allen et al., 2019; Allen et al., 2022).

Several studies have investigated the potential performance-enhancing effect of anti-asthmatic products in athletes. The following sections will provide a concise summary of some key findings.

2.9.1 Are β2-agonists performance-enhancing?

The effect of β2-agonists on performance among healthy athletes have been extensively investigated. A meta-analysis and systematic review by Riiser and colleagues investigated the effect of β2-agonists on aerobic performance among non-asthmatic subjects (2021). The meta-analysis included 47 randomized controlled trials investigating the use of different β2-agonists, including different substances, doses, and administration routes and treatment durations. Overall, β2-agonists were found to have no effect on aerobic performance, which also reflects similar findings in an earlier systematic review on the same topic (Pluim et al., 2011). However, one study found significant improvements in maximal performance when using supratherapeutic dose of salbutamol (Decorte et al., 2013). Overall, the available data suggests that adherence to therapeutic doses of β2-agonists does not enhance performance among healthy athletes.

Koch and colleagues have compared performance enhancing effects of inhaled salbutamol and placebo in asthmatic and non-asthmatic athletes when testing cycling performance (Koch et al., 2015). Although both the asthmatic and non-asthmatic group had a significant improvement in lung function after inhaling salbutamol, there were no improvement in exercise performance from placebo. There was also no difference in physical fitness in the groups before versus after inhaling salbutamol (Koch et al., 2015).

Some of the same authors have investigated the effect of β2-agonists on anaerobic performance (maximal physical performance lasting 1 minute or shorter) in a systematic review and meta-analysis (Riiser et al., 2020). Overall, the analysis showed a 5% increase in performance, which probably would be of importance in sport competitions (Riiser et al., 2020, p. 7). A greater improvement was seen when β2-agonists were taken orally or in supratherapeutic doses. It is therefore unclear whether therapeutic doses of β2-agonists are performance-enhancing, which should be further investigated (Riiser et al., 2020, p. 9).

2.9.2 Are inhaled corticosteroids performance-enhancing?

A meta-analysis and systematic review by Riiser and colleagues investigated the effect of corticosteroids among non-asthmatic subjects (2023). In this meta-analysis, only two of the included randomized controlled trials (RCTs) have investigated the effect of inhaled corticosteroids (ICS) on physical performance among healthy subjects (Jardim et al., 2007; Kuipers et al., 2008). Kuipers and colleagues investigated the performance effect of daily inhalation of 800 μg budesonide or placebo on 28 well-trained cyclists and rowers over 4 weeks. The subjects performed an incremental cycling test to exhaustion at baseline and after two and four weeks, measuring maximal power output (Kuipers et al., 2008, p. 869). The researchers found no significant differences between inhaled budesonide and placebo. However, the authors advised that budesonide should only be prescribed to individuals with medical needs because of its possible side effects and therefor be a potential factor that can decrease performance (Kuipers et al., 2008, p. 870).

The other study was a crossover RCT performed by Jardim and colleagues, who used handgrip and respiratory strength as outcomes in thirteen healthy subjects where 1000 μg flunisolide daily divided into two doses over one month was compared to placebo (2007, p. 1595). The researcher found significant increase handgrip and respiratory strength in both the active flunisolide group and the placebo group, suggesting that there was no performance-enhancing effect of inhaled flunisolide alone (Jardim et al., 2007, p. 1598)

Together, these studies indicate that ICS have no impact on performance among healthy subjects. However, due to few studies with generally small samples, the findings must be interpreted with caution and the problem area requires further investigation.

2.9.3 Are anticholinergics performance-enhancing?

No studies have been found to neither discuss nor examine the potential performance-enhancing effects of anticholinergics.

2.9.4 Are leukotriene receptor antagonists´ performance-enhancing?

There are few studies who have investigated the potential performance-enhancing effects of leukotriene receptor antagonists (LTRA). One study, examining therapeutic doses of Montelukast versus placebo on high intensity submaximal and maximal treadmill exercise in cold temperature among non-asthmatic endurance athletes, found no performance-enhancing effects of Montelukast (Sue-Chu et al., 2000, p. 426). Because of few studies, there is a need for more research on LTRA´s possible effect on performance.

2.10 Anti-doping policy and anti-asthmatic medication

One of the main purposes of the World Anti-Doping Code is to "*protect the athletes fundamental right to participate in doping-free sport and thus promote health, fairness and equality for athletes worldwide"* (World Anti-Doping Agency, 2021, p. 9) As of this, WADA has developed the *Prohibited List of Substances and Methods* that identifies prohibited substances and methods, both within and outside of competitions (World Anti-Doping Agency, 2021, p. 32). There are three criteria for a substance or a method to be included on WADA´s prohibited list: Medical or other scientific evidence indicate that the substance or method (1) *"has potential to enhance or enhances sport performance"*, (2) *"represents an actual or potential health risk to the athlete,* and (3) *"violates the spirit of sport"* (World Anti-Doping Agency, 2021, p. 34). The prohibited list also includes substances and methods that has potential to mask use of other prohibited substances or methods (World Anti-Doping Agency, 2021, p. 34).

Related to LAD, there are restrictions on use of β2-agonists at all times (S3 β2-agonists) (World Anti-Doping Agency, 2024, p. 9). Four substances can legally be used, in restricted doses:

- "*Inhaled salbutamol: maximum 1600 micrograms over 24 hours in divided doses not to exceed 600 micrograms over 8 hours starting from any dose.*
- *Inhaled formoterol: maximum delivered dose of 54 micrograms over 24 hours.*
- *Inhaled salmeterol: maximum 200 micrograms over 24 hours.*
- *Inhaled vilanterol: maximum 25 micrograms over 24 hours."*

These restrictions also include use of β2-agonists combined with ICS as combination products (World Anti-Doping Agency, 2024, p. 9).

Glucocorticoids are prohibited in-competition and belong to group *Glucocorticoids* (S9) on the prohibited list. However, the restriction does not refer to use of ICS (World Anti-Doping Agency, 2024, p. 18). Anticholinergics and LTRA are not included on the prohibited list.

As athletes can experience illnesses or medical conditions that may be related to use of specific treatment with substances or methods noted on the prohibited list, they can apply for *Therapeutic Use Exemption* (TUE) (World Anti-Doping Agency, 2023a, p. 4). The purpose of TUE is to secure athletes´ health when necessary. The requirement to obtain a TUE for the use of substances or methods that are prohibited for performance-enhancement, depends on the athlete´s competitive level as defined by the international federation and national anti-doping organizations (NADOs). For international and national-level athletes, the *International Standard for Therapeutic Use of Exemptions* (ISTUE) requires an application for TUE before usage of a prohibited substance, unless the treatment of the medical condition was urgent or an emergency, cf. article 4.0 ISTUE (World Anti-Doping Agency, 2023a, p. 10). For recreational athletes, it is only necessary to apply retroactively for TUE if there is an *Adverse Analytic Finding* (AAF) (World Anti-Doping Agency, 2023a, p. 12).

Independent of athlete level, there are four main conditions that must be met to obtain TUE for a prohibited substance or methods. Cf. article 4.2 in ISTUE these are; (1) the prohibited substance or method is necessary to treat the medical conditions, (2) the prohibited substance or methods is not performance-enhancing beyond what is expected with normal health, (3) there is no other option which is not included on the prohibited list, and (4) the prohibited substance or method is not a consequence of previous use of prohibited substance or methods (World Anti-Doping Agency, 2023a, p. 11). If these four conditions are not met, the athlete risk an *Anti-Doping Rule Violation* (ADRV).

Depending on the medical condition, there are different guidelines for TUE. For asthma, there are specific diagnostic criteria that must be met. When applying for TUE for asthma, the athlete must be examined by a named specialist and the following criteria must be met:

- A full description of the medical history
- A report of spirometry with flow-volume curve
- If airway obstruction; a positive bronchodilator reversibility test
- If negative reversibility test; a positive bronchial hyperresponsiveness test

For athlete who must reapply for TUE the application must show regular follow-up visits to the specialist (World Anti-Doping Agency, 2023b).

2.11 Use of anti-asthmatic products among athletes

Various statistics on the use of anti-asthmatic products has been reported, with variations likely to be partly attributable to methodological considerations. In the Winter Olympic Games of 2002, 2006, and 2010, the sports of cross-country skiing, Nordic combined, speed skating and biathlon recorded the highest rates of approved use of β2-agonists, ranging for 8.2% to 17.2% (Fitch, 2012, p. 414). For the summer Olympics in 2004 and 2008, the highest use was seen in triathlon, cycling and water sports, varying from 13.1% to 24.9% of the athletes approved for use of β2-agonists. Among the athletes who won individual medals, 11.8-15.6% was approved to use β2-agonists. In sports with a greater risk of LAD, such as swimming and cycling, 17.3-19.3% of the athletes had approval to use β2-agonists, and these athletes accounted for 28.9-32.9% of the individual medals won (Fitch, 2012, p. 415). The same author later reported that among athletes using β2-agonists in 2004, 2006 and 2008, between 69.5-87.2% also used ICS, indicating an increasing trend over the years (Fitch, 2016, p. 153).

Other studies reporting use of anti-asthmatic products, find varying use. Alaranta and colleagues investigated use of medication in Finnish elite athletes compared with a control group (2006). Among the 446 athletes studied, 7% used anti-asthmatic medication, with a higher prevalence observed in female athletes compared to male athletes. Moreover, usage rates were significantly greater among athletes than among control subjects. Highest reported usage was seen in endurance-sports, with 11.1% (Alaranta et al., 2006, pp. 925-926). Locke and Marks investigated the use of anti-asthmatic medication among elite athletes from New Zealand, across various sports who had been diagnosed with asthma (2007). 9% of all the athletes reported to use anti-asthmatics, with higher use among older athletes compared to younger athletes (13% vs. 6%), higher use among females than males (11% vs. 7), and higher use in endurance athletes compared with other athletes (17% vs. 7%) (Locke & Marks, 2007, p. 625). Among the athletes, it was seen an almost double use of SABA compared with LABA. Use of ICS was around the same level as for SABA (Locke & Marks, 2007, p. 625)

Selge and colleagues investigated use of anti-asthmatics between potential German winter Olympic athletes compared with German 2008 summer Olympic athletes based on questionnaires (2016). The findings suggested that 6.8% of the winter athletes and 9.8% of the summer athletes used anti-asthmatic medication without specifying what type (Selge et al., 2016, p. 18). Bernhardsen and colleagues investigated use of anti-asthmatic among Norwegian elite athletes from swimming, cross-country skiing, speed skating, rowing/paddling and ball games (2022). The highest use of anti-asthmatics was seen in cross-country skiers, with 71.9% using ICS, 62.5% using anticholinergics, 43.8% using SABA, 40.6% using LABA and 6.3% using LTRA. Among the other sports there was a high use among rowers/paddlers and swimmers with 13.3-36.4% use of ICS, SABA, and LABA (Bernhardsen et al., 2022, p. 4). Because of a small population, the findings must be considered with caution.

The most recent published data on self-reported use of anti-asthmatic products, is by Gjelstad and colleagues (2023). The authors found that anti-asthmatics were the most reported pharmaceutical products in Norwegian doping control forms (DFCs), together with pain killers. Of the DCFs included, 10.7% contained β2-agonists-products and/or combination products and 10.8% contained ICS-products and/or anticholinergics, with great variation between different sport categories (Gjelstad et al., 2023, p. 06). In this current thesis with the following scientific article, the aim is to further explore the data used by Gjelstad and colleagues, but with focus on the anti-asthmatic products.

2.12 Philosophy of science

Within the natural sciences, the development of knowledge can be viewed through various paradigms based on the epistemological and methodological premises employed to address research findings (Chalmers, 2013, pp. 100-101; Loland & McNamee, 2017, p. 64). Three different paradigms have been identified within sports science: the mechanistic, the hermeneutic, and the critical (Loland & McNamee, 2017, p. 64). Since this study aims to map quantitative data, the findings will be interpreted within a classical paradigm. Following a hypothetical-deductive structure, results from empirical tests will be evaluated against temporary theories and methodological constraints that may affect the validity of the research (Loland & McNamee, 2017, p. 65; Laake et al., 2023, p. 49). Considering dualism, the subjects in this study will be regarded as observable objects, where their opinions and feelings will not be considered significant, as in the interpretive and critical paradigms (Loland & McNamee, 2017, p. 66). In summary, this study will only observe humans from an external perspective, in accordance with the classical paradigm.

3. Methods – Extended

In the following chapter, the extended methods for this thesis will be presented. The main project and study design will be described, as well as an extended description of the data processing and the variables. Lastly, the data collection and ethical considerations will be addressed.

3.1 Main project

The current study is a part of Anti-Doping Norway´s (ADNO) project where the main goal is to investigate the use of pharmaceuticals and dietary supplements among athletes selected for doping control with ADNO from 2015 to 2019 (Gjelstad et al., 2023; Lauritzen & Gjelstad, 2023). In this study, the anti-asthmatic products registered on the doping control forms will be investigated.

3.2 Study design

This study investigates the reported use of anti-asthmatic products based on doping control forms (DCFs) and has an observational cross-sectional design, by evaluate retrospective data.

3.3 Setting

The doping controls were performed between 2015-2019 by personnel from ADNO, in accordance with the International Standard for Testing and Investigation (ISTI) by WADA (World Anti Doping Agency, 2023). Both Norwegian athletes and foreign athletes performing their sport in Norway at events under the auspices of a Norwegian sport federation organized under the Norwegian Confederation of Sport, and Olympic and Paralympic committee were tested.

Results of the present study were based on the DCFs the athletes submit when performing a doping control. In accordance with article 7.4.5. in ISTI, the athlete must submit all pharmaceuticals and dietary supplements taken the previous seven days (World Anti Doping Agency, 2023, p. 51). The included DCFs are stored in ADNOs paper archives in accordance with the World Anti-Doping Code article 14.6 and The Personal Data Act (2018; World Anti-Doping Agency, 2021, pp. 104-105).

3.4 Variables

The database consists of descriptive variables; sex (male; female), age group (<20; 20-24; 25-29; 30-34; 35-40; >40), athlete level (National level athlete or recreational level athlete) and sport category (Ball and team sports; Endurance sports; Strength and power sports; Combat sports; Muscular endurance sports; Gymnastic sports; Aiming sports; Other).

A new variable, describing whether the athletes have high or low risk of developing lower airway dysfunction (LAD) based on the nature of sport, was added to the dataset. The inclusion criteria for high risk of LAD are based on the systematic review and meta-analysis by Price and colleagues (Price et al., 2022). The inclusion criteria are sports with high ventilation demands and exposure for substances that can induce bronchoconstriction, such as trichloramines, cold and dry air, or polluted air. The distribution of low and high risk for LAD are presented in table 1.

Table 1. Distribution of sports with high or low risk to develop lower airway dysfunction

High-risk LAD	Low-risk LAD		
Alpine skiing	Air sport	Dance sport	Power lifting
Athletics	American football	Equaestrian	Rugby
Biathlon	Archery	Fencing	Sailing
Cross-country skiing	Arm wrestling	Fitness center	Shooting
Cycling	Badminton	Floorball	Ski jump
Ice hockey	Bandy	Freeski	Soccer
Nordic combined	Baseball	Frisbee	Squash
Orienteering	Billiard	Functional fitness	Table tennis
Rowing	Bobsleigh & Skeleton	Golf	Taekwondo
Sleddog	Bowling	Gymnastic	Tennis
Snowboard	Boxing	Handball	Volleyball
Speed skating	Canoe	Judo	Waterski
Swimming	Casting	Jujutsu	Weightlifting
Triathlon	Cheerleading	Karate	Wrestling
Telemark	Climbing	Kickboxing	
Underwater sport	Company sport	Lacrosse	
	Cricket	Motorbike	
	Curling	Other	

LAD: Lower airway dysfuntion

The database organized the pharmaceuticals by their Anatomical Therapeutic Chemical Classification Codes (ATC-codes) (World Health Organization, w.y.), and was for the purpose of this study divided into the following subgroups: Short-acting β2-agonsists; Long-acting β2-agonists; Anticholinergics; Inhaled corticosteroids; Leukotriene receptor antagonists (table 2).

Table 2. Pharmaceutical groups based on chemical substance and ATC-codes (5th level)

Pharmaceutical group	Chemical substance	ATC-code (5th level)
Short-acting β2 agonist (SABA)	Salbutamol	R03A C02
	Terbutaline	R03A C03
Long-acting β2 agonist (LABA + LABA in CP)	Salmeterol	R03A C12 or K06
	Formoterol	R03A C13 or K07 or K08 or K11
	Vilanterol	R03A K10
Anticholinergics	Ipratropiumbromid	R03B B01
	Tiotropiumbromid	R03B B04
Inhaled corticosteroids (ICS + ICS in CP)	Beklometason	R03B A01 or R03A K08
	Budesonid	R03B A02 or R03A K07
	Flutikason	R03B A05 or R03A K06 or K011
	Mometason	R03B A07
	Ciklesonid	R03B A08
	Flutikasonfuroat	R03A K10
Leukotriene receptor antagonists (LTRA)	Montelukast	R03D C03

CP: combination products; ATC: Anatomical Therapeutic Chemical Classification

Variables describing the marketed products were also constructed: Short-acting β2-agonsists; Long-acting β2-agonists; Anticholinergics; Inhaled corticosteroids; Leukotriene receptor antagonists; Combination products (Table 3). In addition, a variable was constructed describing the number of products used relating to LAD, by counting the reported number of ATC-codes per DCF. The new and adjusted variables were developed using Microsoft Excel version 16.84 (24041420).

Table 3: Pharmaceutical groups based on marketed products and ATC-code (5th level)

Pharmaceutical group	Chemical substance in products	ATC-code (5th level)
Short-acting β2 agonist (SABA)	Salbutamol	R03A C02
	Terbutaline	R03A C03
Long-acting β2 agonist (LABA)	Salmeterol	R03A C12
	Formoterol	R03A C13
	Vilanterol	R03A K10
Anticholinergics	Ipratropiumbromid	R03B B01
	Tiotropiumbromid	R03B B04
Inhaled corticosteroids (ICS)	Beklometason	R03B A01
	Budesonid	R03B A02
	Flutikason	R03B A05
	Mometason	R03B A07
	Ciklesonid	R03B A08
	Flutikasonfuroat	R03A K10
Combination preparates (LABA + ICS)	Salmeterol and flutikason	R03A K06
	Formoterol and budesonide	R03A K07
	Formoterol and beklometason	R03A K08
	Vilanterol and flutikasonfuroat	R03A K10
	Formoterol and flutikason	R03A K11
Leukotriene receptor antagonists (LTRA)	Montelukast	R03D C03

ATC: Anatomical Therapeutic Chemical Classification

3.5 Bias

To ensure a fully anonymized database, all DCFs from 2015 to 2019 were included. As a result, the reappearance of athletes was undetectable, occurring rarely in the RLA group but more frequently in the NLA group, who consists of athletes in the Registered Testing Pool (RTP) who are tested several times a year (World Anti Doping Agency, w.y.).

3.6 Ethical considerations

Because the database is fully anonymized, written consent was not collected from the athletes selected for doping control. As the study is a collaboration between ADNO and the Norwegian School of Sport Science, both parts signed a collaboration agreement to secure safe use of the database (Appendix 3). This project has been approved by the Regional Committees for Medical and Health Research, ID 29318 (Appendix 4) and by the Norwegian Center of Research Data [Norsk Senter for Forskningsdata (NSD/SIKT)].

3.7 Statistical analysis

To compare categorical variables, Pearson´s Chi-square were used. Analysis of variance (ANOVA) with Bonferroni Posthoc, were used to compare mean use of anti-asthmatic products and substance groups among age groups and sport categories. Mann-Whitney U Test were used to compare numbers of anti-asthmatic products reported between athlete levels. All analysis were performed using IBM SPSS version 28.0. The significance level was set to $p = 0.05$.

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4. Scientific article

4.1 Title page

Manuscript title: Reported use of anti-asthmatic medication in doping control forms from 2015-2019 – mapping retrospective data

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This manuscript is original and not previously published.

4.2 Introduction

Lower airway dysfunction (LAD) is more prevalent among athletes compared to the general population, making it one of the most common medical issues in this group and also a leading cause for the use of medication (Carlsen et al., 2008a; Price, Sewry, et al., 2022; Price, Walsted, et al., 2022). LAD is an umbrella terms that includes exercise-induced asthma (EIA), exercise-induced bronchoconstriction (EIB) and bronchial hyperresponsiveness (BHR) that lack the classical features of asthma (Hull et al., 2021, p. 6; Schwellnus et al., 2022, p. 1090). Thus, whereas exercise generally is being beneficial for people´s health and well-being, there is legitimate concern that prolonged exposure to exercise-induced hyperpnea may negatively impact respiratory health, particularly when performed in high doses and in certain environmental contexts (Bernhardsen, et al., 2022; Støle-Melsom et al., 2022).

Although the etiology and pathophysiology of athletes LAD are incompletely understood and likely to vary between individuals, there is a clear association with endurance training at elite levels. Athletes in sports that involve high volume ventilation and exposure to irritants, such as chlorine, polluted air, or cold and dry air, are known to carry a higher risk (Helenius et al., 1997; Helenius et al., 1998; Støle-Melsom et al., 2022; Couto et al., 2015; Rasmussen et al., 2022). Two different phenotypes have been suggested for LAD, distinguishing between a type 2 and non-type 2 pattern of airway inflammation; the former linked to classical asthma and highly responsive to inhaled corticosteroids, while the latter is more specifically associated with sports-induced asthma (Couto et al., 2015; Tsukioka et al., 2017; Rasmussen et al., 2022, p. 4). Further the parasympathetic nervous system has also been suggested to be implicated in the mechanism of development of asthma, opening for the use of anticholinergic medication (Knöpfli & Bar-Or, 1999; Stang et al., 2016).

Despite its heterogeneity and complex etiology, there is agreement that athletes´ LAD should be treated according to the asthma guidelines that apply to the general population (Carlsen et al., 2008b; GINA, 2023). These recommendations include both self-management strategies, which for an athlete would involve considering exposures to the triggers of the respiratory symptoms, as well as medical treatment. The guidelines prescribe a stepwise approach to treatment, involving increasing doses and gradual addition of multiple medications based on the severity of symptom and illness (GINA, 2023, p. 58-65). For athletes, such escalation poses a risk of encountering doses or substances that are subject to doping regulations (World Anti-doping Agency, 2024). While anticholinergic, inhaled corticosteroids (ICS), and leukotriene receptor agonists (LTRA) are permitted, certain inhaled β2-agnoists are only allowed in restricted doses (World Anti-doping Agency, 2024). Use outside these regulations requires a Therapeutic Use Exemption (TUE) (World Anti-doping Agency, 2023a). A recent study found that anti-asthmatics were the most frequently used class of medication among athletes, along with painkillers (Gjelstad et al., 2023, p. 6), supported by earlier literature highlighting a high level of use among particularly endurance athletes (Bernhardsen et al., 2022; Fitch, 2012, 2016; Price, Sewry et al., 2022).

Poorly managed LAD can prevent affected individuals from exercising and disrupt sports careers, posing challenges not only affected individuals but also for society at large due to its prevalence and widespread impact (Carlsen, et al., 2008b, 493). We therefor need to understand how asthma medications are used by athletes, not only among elite athletes, but also among recreational athletes. Thus, our aim was to detail the use of asthma medication as documented in doping control forms (DCFs) obtained during test sessions conducted in both recreational and elite athletes in Norway, covering the years from 2015 to 2019.

4.3 Methods

This study investigates the use of anti-asthmatic medication based on DCFs obtained during 2015 to 2019, using an observational cross-sectional design, mapping retrospective data.

The doping control forms were obtained between 2015-2019 by personnel from Anti-Doping Norway (ADNO), in accordance with the International Standard for Testing and Investigation (ISTI) by WADA (World Anti-doping Agency, 2023b). Both Norwegian and foreign athletes performing their sport in Norway at events under the auspices of a Norwegian sport federation organized under the Norwegian Confederation of Sport, and Olympic and Paralympic Committee were tested.

Results of the present study are based on the DCFs the athletes submit when performing a doping control. In accordance with article 7.4.5 in ISTI, the athlete must submit all pharmaceuticals and dietary supplements taken the previous seven days (World Anti-doping agency, 2023b, p. 51). The included DCFs are stored in ADNOs own paper archives in accordance with the World Anti-Doping Code article 14.6 and The Personal Data Act (2018; World Anti-Doping Agency, 2021, p. 104-105).

A dataset was constructed based on the DCFs, consisting of descriptive variables; Sex (male; female), age groups (<20; 20-24; 25-29; 30-34; 35-40; >40), athlete level (national level athlete; recreational level athlete) and sport category (Ball and team sports; Endurance sports; Strength and power sports; Combat sports; Muscular endurance sports; Gymnastic sports; Aiming sports; Other).

A variable was constructed to identify whether athletes were engaged in a sport considered to represent a high risk of developing LAD, based on the systematic review and meta-analysis by Price and colleagues; i.e., sports that demand high volume ventilation and exposure to environmental conditions and substances that can induce bronchoconstriction, such as cold and dry air, polluted air and chlorine products (Price, Sewry et al., 2022). Examples of sports classified as high risk are cross-country skiing, biathlon, swimming, triathlon, e.g. Examples of sports classified as low risk are boxing, soccer, dancing, climbing, e.g.

The database organized the pharmaceuticals by their ATC-codes (World Health Organization, w.y.) and was for the purpose of this study divided into the following subgroups: Short acting ß2-agonists; Long acting ß2-agonists; Anticholinergics;

Leukotriene receptor antagonists; Inhaled corticosteroids. Variables describing the marketed products were also constructed; Short acting ß2-agonists; Long acting ß2-agonists; Anticholinergics; Inhaled corticosteroids; Combination products; Leukotriene receptor antagonists. In addition, a variable was constructed describing the number of anti-asthmatic products, by counting the reported number of ATC-codes per DCF.

To ensure a fully anonymized database, all DCFs from 2015 to 2019 were included. As a result, the reappearance of athletes could not be detected, a phenomenon occurring rarely in the RLA group but more frequently in the NLA group, who consists of athletes in the Registered Testing Pool (RTP) and are tested several times a year.

Because the database is fully anonymized, written consent was not collected from the athletes selected for doping control. As the study is a collaboration between ADNO and the Norwegian School of Sport Science, both parts signed a collaboration agreement to secure safe use of the database. The project has been approved by the Regional Committees for Medical and Health Research, ID 29318.

To compare categorical variables, Pearson´s Chi-square were used. Analysis of variance (ANOVA) with Bonferroni Posthoc were used to compare mean use of anti-asthmatic products and substance groups among age groups and sport categories. Mann-Whitney U Test were used to compare numbers of anti-asthmatic products between athlete levels. All analysis were performed using IBM SPSS, version 28.0. The significance level was set to $p = 0.05$.

4.4 Results

A total of 10 418 doping control forms (DCFs) were included, representing all DCFs sustained by Anti-Doping Norway during 2015 through 2019. Of all DCFs, 1702 (16.3%) contained one or more anti-asthmatic products (Table 2). Split by substance group as well as product category, bronchodilators were the most frequently reported anti-asthmatic (Table 3 and 4).

Table 1. Frequencies of doping control forms included in the study, split by categories.

Factor	Category	**Total**	Age distribution					
			<20	20-24	25-29	30-34	35-39	>40
Sex	Female	2470	376	805	883	214	100	101
	Male	7939	1086	2814	2476	1051	267	245
Athlete level	RLA	4234	958	1419	1053	386	174	244
	NLA	6184	504	2200	2306	879	193	102
Sport Category	Aiming sports	106	27	24	20	8	5	22
	Ball and team sports	4057	689	1569	1246	429	103	21
	Fighting sports	799	200	349	140	70	26	14
	Gymnastics sports	130	38	55	32	3	1	1
	Muscular endurance sports	184	7	53	80	37	7	0
	Strength and power sports	1758	203	548	616	219	94	78
	Endurance sports	3233	272	990	1187	482	112	190
	Other	151	26	31	38	17	19	20
Risk	Low	5748	1059	2096	1637	625	202	129
	High	4670	403	1523	1722	640	165	217
Total		10418	1462	3619	3359	1265	367	346

RLA: recreational level athlete, NLA: National level athlete

4.4.1 By sex

There were 2479 DCFs from females and 7939 from males (Table 1), with 18.3% of the female´s DCFs reporting one or more anti-asthmatic product compared to 15.6% of the male´s (p <0.01) (Table 2). Among the DCFs reporting one or more anti-asthmatic product, the use of two products were most frequently reported among females, while males most frequently reported the use of one product. Anticholinergics were the most frequently reported bronchodilator among females, while short acting β2-agonists (SABA) were most reported among DCFs from males. In both sexes, inhaled corticosteroids (ICS) were the most frequently reported anti-inflammatory medicine (Table 3).

Table 2. Number of doping control forms reporting anti-asthmatic products, split by sex, athlete level and risk.

Number of products per form	Total	Sex		Athlete level		Risk	
		Female	Male	RLA	NLA	Low	High
0	8716	2023	6693	3902	4814	5436	3280
1	686	154	532	194	492	185	501
2	619	211	408	97	522	107	512
3	273	62	211	32	241	19	254
4	78	27	51	8	70	1	77
5	37	2	35	1	36	0	37
6	5	0	5	0	5	0	5
7	4	0	4	0	4	0	4
Total ≥1	1702	456	1246	332	1370	312	1390
Total	10418	2479	7939	4234	6184	5748	4670
P-values		p<0.01		p<0.01		p<0.01	

RLA: recreational level athlete, NLA: National level athlete

4.4.2 By age group

The age groups 25-29 years and 30-34 years were the most frequently reported, representing 34.7% and 32.2% of the DCFs respectively. The mean number of products reported is found to increase significantly between the younger age groups up to a peak mean of 0.48 products reported in the age group 30-34 years, before the mean number decrease significantly in the older age groups (Figure 1A, all p <0.01). Split by substance group, SABA was the most common bronchodilator among age group <20, 20-24 and >40. Among age group 25-29, 30-34 and 35-39 the most reported bronchodilator were anticholinergics. The least reported bronchodilator product was long acting β2-agonists (LABA), except for the age group 35-39 years and >40 years were SABA and anticholinergics respectively were the least reported (Table 3).

4.4.3 By athlete level

The distribution of DCFs among recreational level athlete (RLA) and national level athlete (NLA) were 40.6% and 59.4% respectively (Table 1). NLA reported a significantly higher use of anti-asthmatic products, with 22.2% of DCFs from NLA containing one or more product, while the number for RLA were 7.8% (p <0.01). Among DCFs from NLA the most frequent number of products reported was two, while

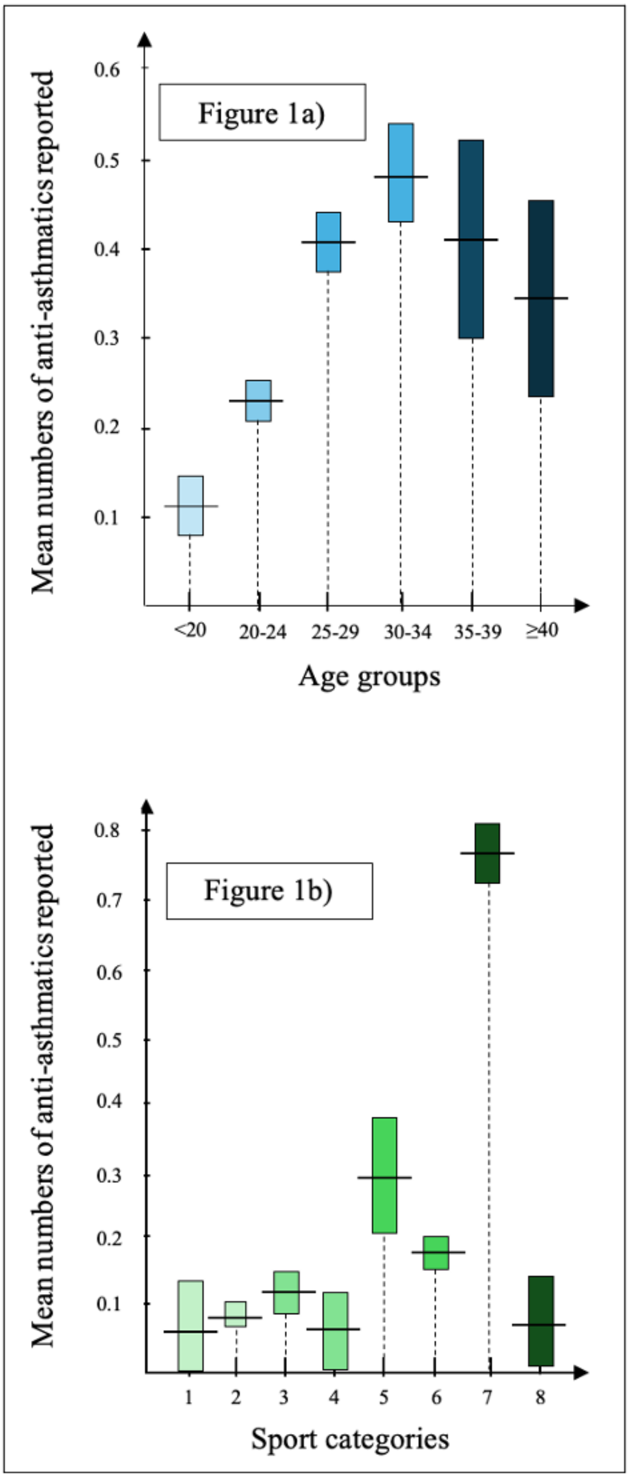

Figure 1a/b. Mean numbers (SD) of anti-asthmatic products reported per doping control form.

1 = Aiming sports; 2 = Ball and team sports; 3 = Fighting sports;
4 = Gymnastics sports; 5 = Muscular endurance sports;
6 = Strength and power sports; 7 = Endurance sports; 8 = Other sports

RLA most frequently reported one product (Table 2). Split in substance group, the most reported bronchodilator among NLA were anticholinergics, while among RLA it was SABA. For both athlete levels ICS were the most reported anti-inflammatory medicine (Table 3).

In DCFs reported from NLA, it was significantly higher use of all products independent of number of total anti-asthmatic products registered (all p <0.01), except for DCFs from RLA reporting higher use of one SABA product alone (p <0.01) (Table 4). Split by substance group, anticholinergics is the most frequently reported bronchodilator product among NLA, while SABA were most frequently reported by RLA. Among anti-inflammatory products, ICS was most reported both in NLA and RLA. Combination products were most frequently reported by RLA (n = 121). The most common anti-inflammatory and bronchodilator combination reported in DCFs from

NLA were ICS and anticholinergics, which was more frequently reported than combination products (Table 4). The highest number of reported products were seen in DCFs belonging to NLA, with four separate forms reporting seven products.

Table 3. Number of doping control forms reporting use of the respective pharmaceutical substance group within age groups, sport category, sex, athlete level and risk.

Factor	Category	Bronchodilators			Anti-inflammatory	
		SABA	LABA	Ach	ICS	LTRA
Age groups	<20	75	28	29	51	12
	20-24	236	188	213	314	50
	25-29	283	218	420	516	54
	30-34	143	104	163	221	19
	35-39	30	32	38	55	8
	>40	31	25	19	32	17
Sport category	Aiming sports	1	2	1	3	0
	Ball and team sports	165	99	16	127	25
	Fighting sports	46	20	14	29	0
	Gymnastics sports	4	1	1	2	0
	Muscular endurance sports	8	2	14	31	0
	Strength and power sports	69	46	75	115	24
	Endurance sports	499	423	761	879	110
	Other	6	2	0	3	1
Sex	Female	151	110	281	327	58
	Male	647	485	601	862	102
Athlete level	RLA	239	130	48	181	33
	NLA	559	465	834	1008	127
Risk	Low	210	131	39	175	22
	High	588	464	843	1014	138
Total		798	595	882	1189	160
		2725			1349	

RLA: Recreational level athlete, NLA: National level athlete, SABA: Short acting β2-agonist: LABA: Long acting beta 2 agonist, ICS: Inhalation corticosteroids, CP: combination preparate, Ach: Anticholinergics, LTRA: Leukotriene receptor antagonists

4.4.4 By sport category

The most common sport categories reported on DCFs were ball and team sports and endurance sports, representing 38.9% and 31% respectively (Table 1). DCFs from endurance sports had the highest mean number of reported products compared with the other sprot categories (mean: 0.77, p <0.01) (Figure 1b). Muscular endurance sports were the sport category with second highest mean number of products, significantly higher than aiming, ball and team, fighting, gymnastics and other sports (p <0.01) (Figure 1b).

Split by substance groups, athletes in endurance sports reported significantly higher use of all products compared with athletes in the other sport categories (all *p* <0.01) (Table 3). Among all sport categories, ICS were the most frequently reported anti-inflammatory medicine, being most frequently reported in DCFs belonging to endurance sport athletes. In ball and team, fighting, gymnastics, and other sports, SABA were the most frequently reported bronchodilator medicine. Anticholinergics were the most frequently reported bronchodilator medicine among endurance, strength and power, and muscular endurance sport athletes. Only in aiming sport, LABA were the most frequently reported bronchodilator (Table 3).

Table 4. Number of doping control forms reporting asthma-related products split by athlete level.

Number of products per form	Bronchodilators			Anti-inflammatory		Combination			
	SABA	LABA	Ach	ICS	LTRA	SABA + ICS**	LABA + ICS**	Ach + ICS**	CP***
RLA									
1	127*	3	8	10	4	-	-	-	42
2	78	1	16	30	7	23	0	7	60
3	25	5	18	20	14	15	5	13	13
4	8	1	5	5	7	5	1	2	5
5	1	0	1	1	1	1	0	1	1
6	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0
Total	239	10	48	66	33	44	6	23	121
NLA									
1	85	0	199	72	20	-	-	-	116
2	203	27	313*	338	20	83	9	231	135
3	278	38	210	284	31	127	37	167	61
4	52	35	67	62	29	44	33	59	10
5	32	33	36	36	18	32	33	36	3
6	5	5	5	5	5	5	5	5	0
7	4	4	4	4	4	4	4	4	0
Total	559	142	834	701	127	295	121	502	325
	1535			828		1243			
P-values	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01

RLA: Recreational level athlete, NLA: National level athlete, SABA: Short acting β2-agonist: LABA: Long acting β2 agonist, ICS: Inhalation corticosteroids, CP: combination preparate, Ach: Anticholinergics, LTRA: Leukotriene receptor antagonists

*= Example RLA/SABA/1: DCFs reported by RLA containing one product and this being SABA-product. Example NLA/Ach/2: DCFs reported by NLA containing two product and at least one of this being Ach-product.

**=SABA/LABA/Ach+ICS represents forms reporting at least one bronchodilator and one anti-inflammatory product. Ex. Ventoline®/Serevent®/Atrovent® + Flutide®

***=combination products represent products containing both bronchodilators and anti-inflammatory substances. Ex. Inuxair® or Seretide®

4.4.5 By risk for asthma

Of 10 418 DCFs, 44.8% belonged to athletes with higher risk to develop LAD (Table 1). DCFs from athletes in high-risk sports reported a significantly higher number of anti-asthmatic products compared with low-risk sports (*p* <0.01) (Table 2). Among high-risk sports, 29.7% of the DCFs contained one or more product, whereas the percentage were 5.4% for DCFs for low-risk sport. Among the DCFs belonging to high-risk athletes who used anti-asthmatic products, the use of two products were most frequently reported, while for the low-risk athlete one product was most frequently reported (Table 2). Split by substance group, anticholinergics were the most reported bronchodilator among high-risk athletes, while it was SABA among low-risk athletes. For both groups ICS were the most frequently reported anti-inflammatory medicine (table 3).

4.5 Discussion

4.5.1 Key results

10 418 doping control forms (DCFs) were included in this study, and of these 1702 (16.3%) reported one or more anti-asthmatic product (Table 2). DCFs from national level athletes (NLA) and endurance athletes contained the highest number of products compared with recreational level athletes (RLA) and other sport categories, respectively (p <0.01). The most reported anti-inflammatory medicine was inhaled corticosteroids (n = 701), the same for the most common substance groups reported (n = 1189). Both split in use of product and substance groups anticholinergics were the most reported bronchodilator overall (n = 882) (Table 4). Split by athlete level the most used bronchodilator among RLA were short acting β2-agonists (SABA) (n = 239), while for NLA it was anticholinergics (n = 834).

4.5.2 Interpretation

Of 10 418 DCFs, 16.3% reported one or more anti-asthmatic products (Table 2). Research on the utilization of anti-asthmatic products remains limited. Fitch examined the approved usage of β2-agonists among Olympic athletes and discovered approval rates ranging from 4.2% to 7.8% between 2002 and 2010 (2012, p. 415; 2016, p. 154). Alaranta and colleagues found that 7% of 446 elite Finnish athletes reported use of anti-asthmatic products (2006, p. 921). Locke and Marks observed that 9% of 424 elite athletes from New Zealand reported using anti-asthmatic products (2007, p. 625). A possible reason for the number in this study being higher compared to other, may be explained by difference in sample-size. In addition, reappearance of the same athlete on different DCFs may affect the results.

As found by Gjelstad and colleagues, anti-asthmatic products are the most frequently reported pharmaceuticals among DCFs (2023, p. 5). This reflects LAD being one of the most common health problems among athletes (Rasmussen et al., 2022; Støle-Melsom et al., 2022). A recent comprehensive examination of LAD prevalence among athletes, found that the overall prevalence rate over the three past decades (since 1990) is estimated to be 21.8% (Price, Sewry, et al., 2022, p. 3). A higher prevalence of 25.1% was seen in athletes from endurance sports compared to other sports, similar to findings in the present study (p. 8). Compared to other studies investigating use of anti-asthmatic products, the result from this study is more similar to the prevalence of LAD. A sensible finding considering the likelihood of athletes with LAD using asthma medication (Alaranta et al., 2006; Locke and Marks, 2007; Fitch, 2012; 2016; Bernhardsen et al., 2022).

Among 2479 DCFs submitted by female athletes, 18.3% indicated the presence of one or more anti-asthmatic product, a proportion significantly greater than observed among male athletes (15.6%). This trend aligns with findings reported by Gjelstad et al., wherein a significantly higher prevalence of general pharmaceutical usage among females compared to males was identified (2023, p. 8). The findings also reflect the LAD prevalence among athletes, where the prevalence among females is overall higher compared to men (Price, Sewry, et al., 2022, p. 5). However, investigations exploring the reported use of anti-asthmatic products across sexes remain few. Notably, Locke and Marks observed a significantly higher prevalence of anti-asthmatic product usage among females, reflecting the same distribution pattern observed in the present study (2007, p. 625). Nevertheless, while consistent with our findings, the overall prevalence reported by Locke and Marks appears lower, potentially attributed to disparities in sample size and the reappearance of athletes in DCFs within the current study.

An increase in mean number of reported products was observed with age, were age group 30-34 years showing the highest use. This may be explained by the higher risk for develop LAD after many years of excessive high-intensive training (Ali et al., 2012; Cockcroft, 2010; Couto et al., 2018; Kippelen et al., 2018). This observation aligns with findings by Locke and Marks, who similarly noted a heightened prevalence of product utilization among older athletes relative to their younger counterparts (2007, p. 625). However, the age groups included in this study are older compared to the study from Locke and Marks where the oldest age group was 25-30 years.

National level athletes report a higher use of anti-asthmatic products compared with RLA (Table 4). This reflects the results in the article by Gjelstad and colleagues finding a higher reported use of pharmaceuticals among DCFs from NLA compared with RLA (2023). To our knowledge, no other studies have compared the use of anti-asthmatic products between NLA and RLA, and there are no studies mapping the use of anti-asthmatic products in RLA alone. Interestingly, DCFs from RLA contain single use of one SABA product more often than NLA (Table 4). Since 2019 GINA guidelines discourage monotherapy with SABA in treatment of asthma due to possible negative health outcomes when not including ICS in medical treatment (GINA, 2023, Kaplan et al., 2020). As the data in this current study was collected before the change of GINA guidelines, the new recommendations may have induced a shift in the practice, and consequently also patterns of use. Future studies should re-examine this in light of the new guidelines.

The most reported bronchodilator was anticholinergics (Table 3 and 4), a result also found by Bernhardsen and colleagues (2022). Among cross-country skiers, they identified anticholinergics as the predominant bronchodilator, with self-reported usage rates of 62.5%, followed by 43.8% for SABA, and 40.6% for LABA (2022, p. 4). Conversely, β2-agonists were more prevalent among rowers and swimmers compared to anticholinergics. The discrepancies in reported use could be affected by reappearance of athletes in the present study, as well as differences in division in subcategories. Nevertheless, given that DCFs do not necessarily correspond to individual athletes, caution should be exhibited when interpreting discrepancies in reported frequencies of anti-asthmatic product usage.

The are several possible explanations for why anticholinergics are the most frequently reported bronchodilator. Some studies suggest that increased parasympathetic activity may be a cause for BHR among athletes (Knöpfli & Bar-Or, 1999; Stang et al., 2016). Increased parasympathetic activity leads to a release of acetylcholine binding to muscarinic receptors, consequently leading to bronchoconstriction. As anticholinergics block the muscarinic receptors, the substance prevents acetylcholine from binding and initiation bronchoconstriction (Knöpfli & Bar-Or, 1999, Legemiddelhåndboka [Handbook of pharmaceuticals], 2023). If increased parasympathetic activity contributes to BHR in athletes, the higher prevalence of anticholinergic usage might be attributed to the greater symptom relief they provide compared to β2-agonists. As the DCFs do not contain health information about the athlete, uncertainties exist regarding the phenotype linked to the DCF and thereby also which medication should be most effective in theory. Another possible explanation for anticholinergics being the most frequently reported bronchodilator, can be as simply as it is not listed on WADAs prohibited list, in contrast to β2-agonists (World Anti-Doping Agency, 2024). In addition, to our knowledge no studies have investigated the possible performance-enhancing effect of anticholinergics. Further studies should investigate both the possible underlying benefits for using anticholinergics as bronchodilators among athletes, as well as the possible performance-enhancing effect to secure both health and fair play in sports.

The highest mean number of reported products was seen among endurance athletes and reflects the higher prevalence of LAD among this group compared with other sports (Price, Sewry, et al., 2022). Just like the higher use among older age groups, this may be explained by the large volumes of high-intensive training over several years. In addition, several of the DCFs in this category comes from athletes doing sport that exposed them for bronchial irritants, such as cold and dry air, polluted air, and trichloramines from swimming pools, leading to higher risk to develop LAD (Støle-Melsom et al., 2022, p. 7). This may also explain why muscular endurance sports had the second highest mean number of reported products, as this includes sports such as speed skating and alpine skiing where exposure to irritants such as dry and cold air is common.

Split by the potential risk for LAD, 29.7% of the DCFs from athletes in high-risk sports contained one or more anti-asthmatic products, while the number was 5.4% among athletes from low-risk sports. This reflects the prevalence of LAD among high- and low-risk sports, where sports with high ventilation demands and exposure for bronchial triggers are of high risk to develop LAD. Bernhardsen and colleagues found a significantly higher use of anti-asthmatic products among typically high-risk sports, compared to ball and team sports, reflecting the same findings as in this study (2022, p. 4).

4.5.3 Limitations

While the study benefits from a substantial sample size, a significant limitation lies in the fact that the DCFs do not directly correspond to individual athletes. Consequently, the same athlete may have submitted several DCFs, thereby skewing the results. The NLA group is anticipated to have a greater number of reappearances, primarily due to the likelihood of including athletes from RTPs. Athletes within RTPs, designated as top or national level athletes by their respective sport federations, are always obligated to state whereabouts information and undergo multiple tests a year (World Anti-Doping Agency, w.y.). Consequently, the generalizability within this cohort is likely reduced compared to RLA, where athletes are less frequently subjected to multiple tests. Nonetheless, it is plausible that RLA athletes may also undergo testing on multiple occasions in certain instances.

As the database is fully anonymized, the results are based on self-reported usage of anti-asthmatic products, thereby enabling reporting bias as a possible limitation. As mentioned by Gjelstad et al., the doping control process can induce stress in athletes, potentially leading to forgetfulness and underreporting (2023, p. 9). Simultaneously, it is worth considering whether some athletes may overreport out of an abundance of caution. If necessary, athletes do have the option to submit post-registration to ADNO. However, nor data pertaining to post-registration or urine test results are included in this study due to its complete anonymization.

4.6 Conclusion

Among doping control forms from 2015-2019, 16.3% contained one or more anti-asthmatic product. The most used bronchodilator were anticholinergics, while inhaled corticosteroids were the most used anti-inflammatory substance. Female athletes reported significantly higher use compared to men, together with NLA and athletes classified as high-risk for LAD. Age-group 30-34 and endurance athletes had the highest mean number of reported products on DCFs compared with other age group and sport categories. The current study is limited by methodological constraints as DCFs may represent the same athletes doping controlled several times in the period. In the light of few other studies and missing health information about the athletes representing the DCFs, further studies should investigate the medication pattern among athletes related to different phenotypes. Further research may give valuable information about the medication pattern in athletes, which also be of value in the development of LAD guidelines in athletes.

4.7 Acknowledgement

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Table overview

Extended methods:

Table 1. Distribution sports with high or low risk to develop lower airway dysfunction.

Table 2. Pharmaceutical groups based on chemical substance and ATC-codes (5th level)

Table 3. Pharmaceutical groups based on marketed products and ATC-code (5th level)

Scientific article:

Table 1. Frequencies of doping control forms included in the study, split by categories.

Table 2. Number of doping control forms reporting anti-asthmatic products, split by sex, athlete level and risk.

Table 3. Table 3: Number of doping control forms reporting use of the respective pharmaceutical substance group within age groups, sport category, sex, athlete level and risk.

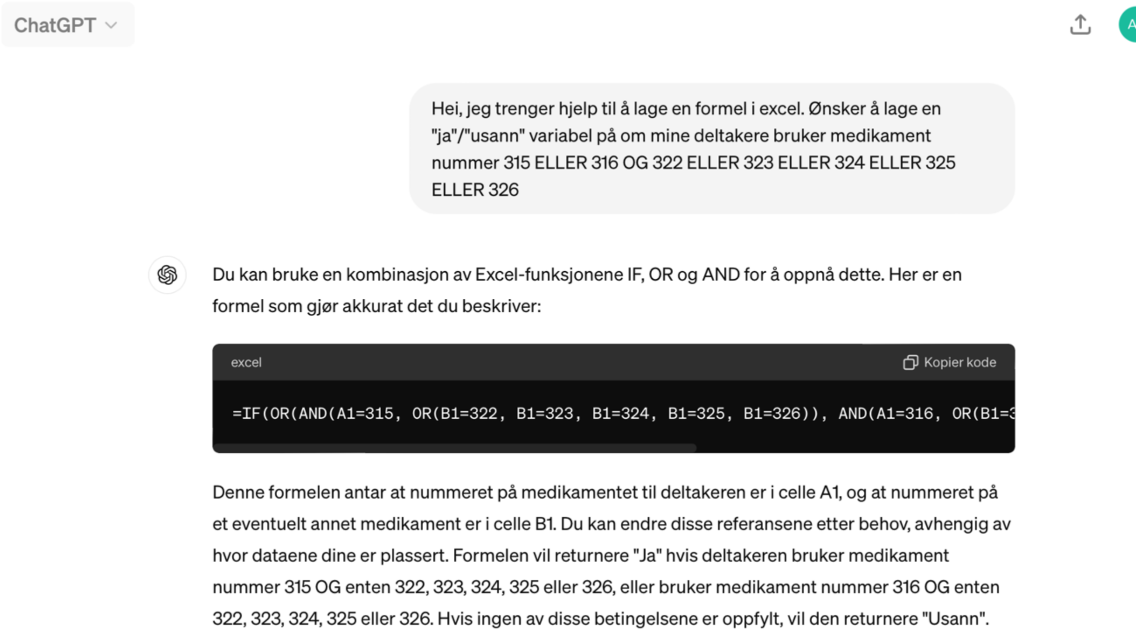
Table 4. Number of doping control forms reporting asthma-related products split by athlete level.

Figures overview

Scientific article:

Attachments

4.8 Appendix 1: Use of artificial intelligence (AI) to produce formulas in excel for data handling (in Norwegian)

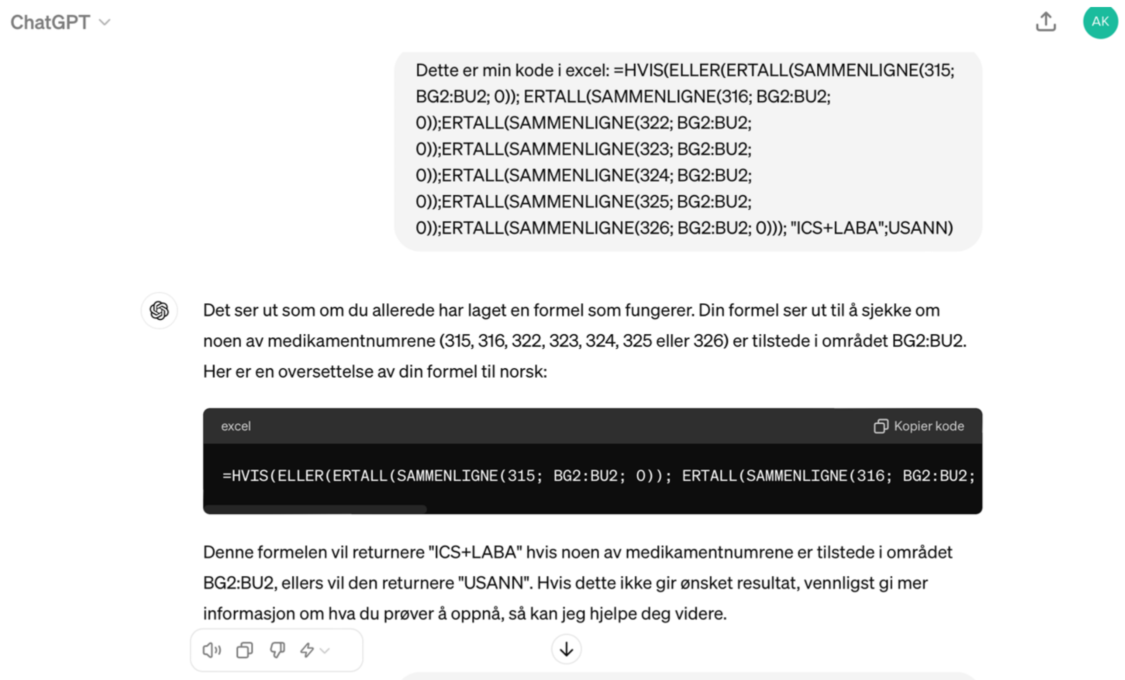


Hei, jeg trenger hjelp til å lage en formel i excel. Ønsker å lage en "ja"/"usann" variabel på om mine deltakere bruker medikament nummer 315 ELLER 316 OG 322 ELLER 323 ELLER 324 ELLER 325 ELLER 326

Du kan bruke en kombinasjon av Excel-funksjonene IF, OR og AND for å oppnå dette. Her er en formel som gjør akkurat det du beskriver:

```excel
=IF(OR(AND(A1=315, OR(B1=322, B1=323, B1=324, B1=325, B1=326)), AND(A1=316, OR(B1=3
```

Denne formelen antar at nummeret på medikamentet til deltakeren er i celle A1, og at nummeret på et eventuelt annet medikament er i celle B1. Du kan endre disse referansene etter behov, avhengig av hvor dataene dine er plassert. Formelen vil returnere "Ja" hvis deltakeren bruker medikament nummer 315 OG enten 322, 323, 324, 325 eller 326, eller bruker medikament nummer 316 OG enten 322, 323, 324, 325 eller 326. Hvis ingen av disse betingelsene er oppfylt, vil den returnere "Usann".

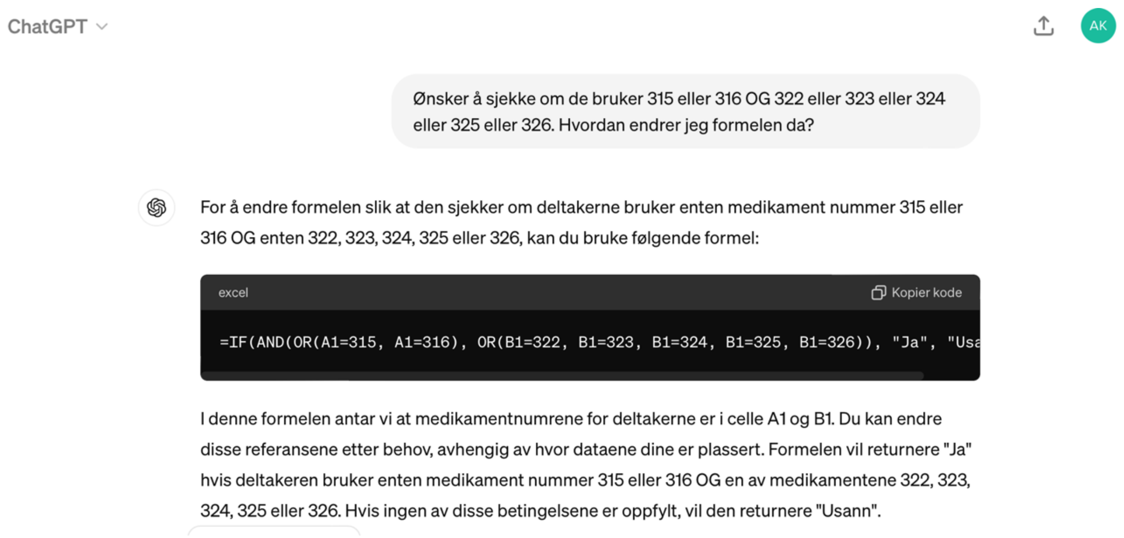


Dette er min kode i excel: =HVIS(ELLER(ERTALL(SAMMENLIGNE(315; BG2:BU2; 0)); ERTALL(SAMMENLIGNE(316; BG2:BU2; 0));ERTALL(SAMMENLIGNE(322; BG2:BU2; 0));ERTALL(SAMMENLIGNE(323; BG2:BU2; 0));ERTALL(SAMMENLIGNE(324; BG2:BU2; 0));ERTALL(SAMMENLIGNE(325; BG2:BU2; 0));ERTALL(SAMMENLIGNE(326; BG2:BU2; 0))); "ICS+LABA";USANN)

Det ser ut som om du allerede har laget en formel som fungerer. Din formel ser ut til å sjekke om noen av medikamentnumrene (315, 316, 322, 323, 324, 325 eller 326) er tilstede i området BG2:BU2. Her er en oversettelse av din formel til norsk:

```excel
=HVIS(ELLER(ERTALL(SAMMENLIGNE(315; BG2:BU2; 0)); ERTALL(SAMMENLIGNE(316; BG2:BU2;
```

Denne formelen vil returnere "ICS+LABA" hvis noen av medikamentnumrene er tilstede i området BG2:BU2, ellers vil den returnere "USANN". Hvis dette ikke gir ønsket resultat, vennligst gi mer informasjon om hva du prøver å oppnå, så kan jeg hjelpe deg videre.



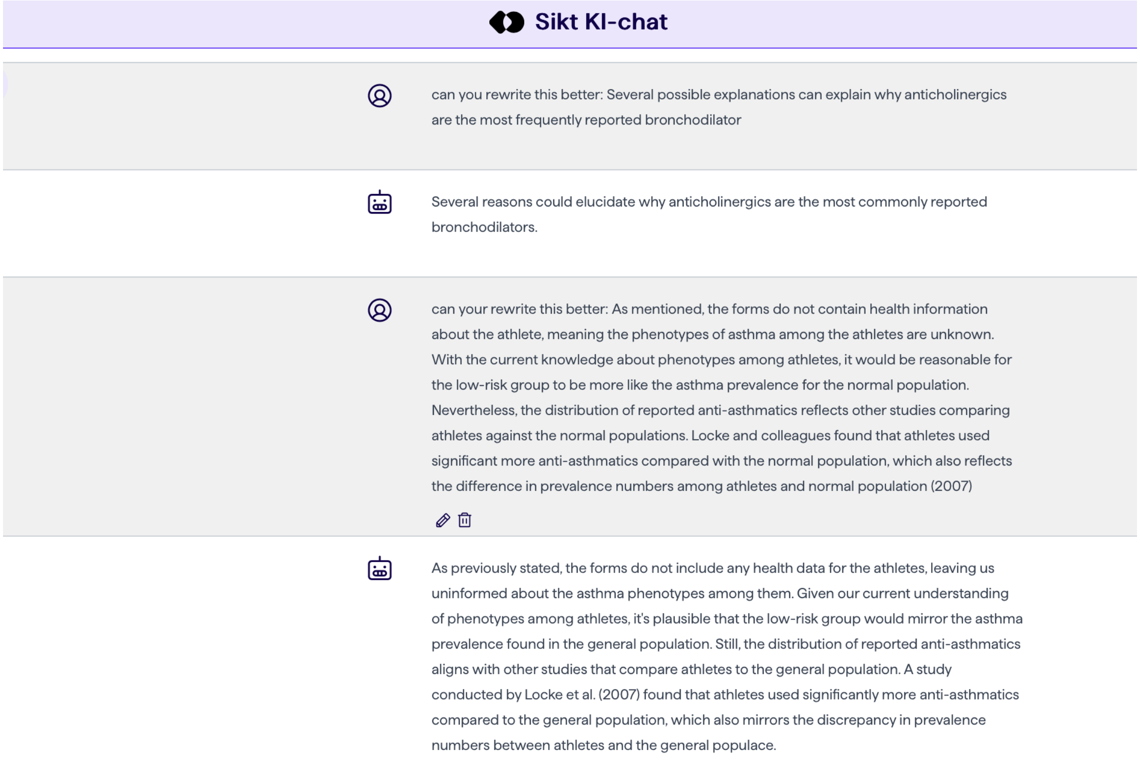
Ønsker å sjekke om de bruker 315 eller 316 OG 322 eller 323 eller 324 eller 325 eller 326. Hvordan endrer jeg formelen da?

For å endre formelen slik at den sjekker om deltakerne bruker enten medikament nummer 315 eller 316 OG enten 322, 323, 324, 325 eller 326, kan du bruke følgende formel:

```excel
=IF(AND(OR(A1=315, A1=316), OR(B1=322, B1=323, B1=324, B1=325, B1=326)), "Ja", "Usa
```

I denne formelen antar vi at medikamentnumrene for deltakerne er i celle A1 og B1. Du kan endre disse referansene etter behov, avhengig av hvor dataene dine er plassert. Formelen vil returnere "Ja" hvis deltakeren bruker enten medikament nummer 315 eller 316 OG en av medikamentene 322, 323, 324, 325 eller 326. Hvis ingen av disse betingelsene er oppfylt, vil den returnere "Usann".

4.9 Appendix 2: Use of artificial intelligence for spelling/phrasing (examples)

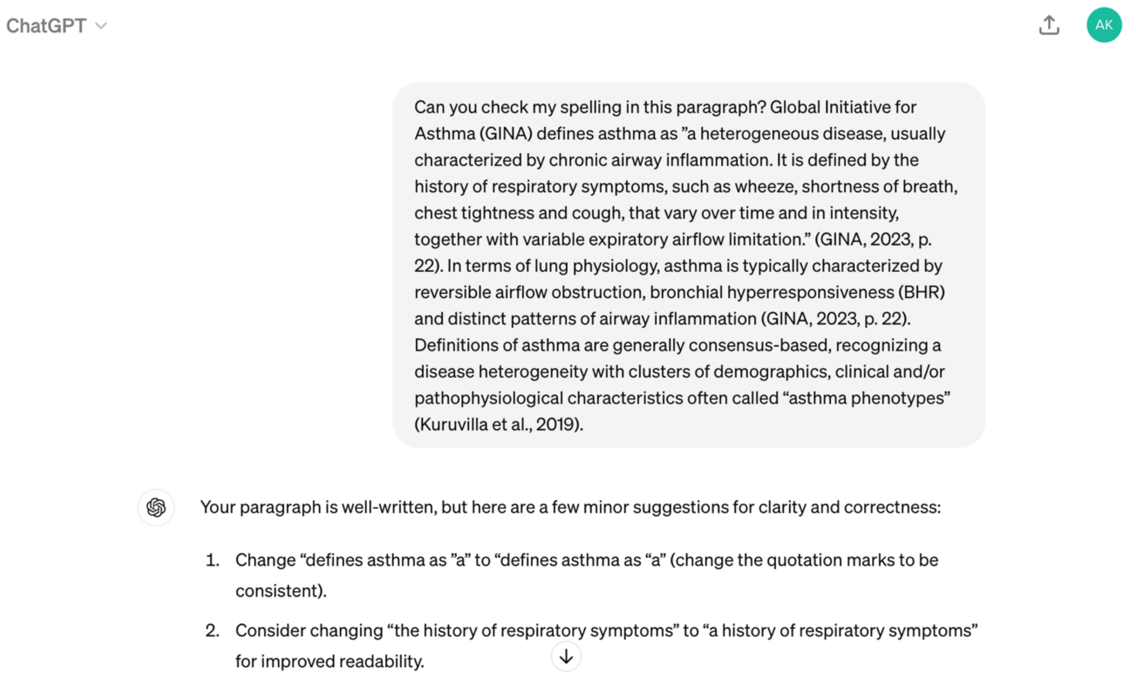


can you rewrite this better: Several possible explanations can explain why anticholinergics are the most frequently reported bronchodilator

Several reasons could elucidate why anticholinergics are the most commonly reported bronchodilators.

can your rewrite this better: As mentioned, the forms do not contain health information about the athlete, meaning the phenotypes of asthma among the athletes are unknown. With the current knowledge about phenotypes among athletes, it would be reasonable for the low-risk group to be more like the asthma prevalence for the normal population. Nevertheless, the distribution of reported anti-asthmatics reflects other studies comparing athletes against the normal populations. Locke and colleagues found that athletes used significant more anti-asthmatics compared with the normal population, which also reflects the difference in prevalence numbers among athletes and normal population (2007)

As previously stated, the forms do not include any health data for the athletes, leaving us uninformed about the asthma phenotypes among them. Given our current understanding of phenotypes among athletes, it's plausible that the low-risk group would mirror the asthma prevalence found in the general population. Still, the distribution of reported anti-asthmatics aligns with other studies that compare athletes to the general population. A study conducted by Locke et al. (2007) found that athletes used significantly more anti-asthmatics compared to the general population, which also mirrors the discrepancy in prevalence numbers between athletes and the general populace.

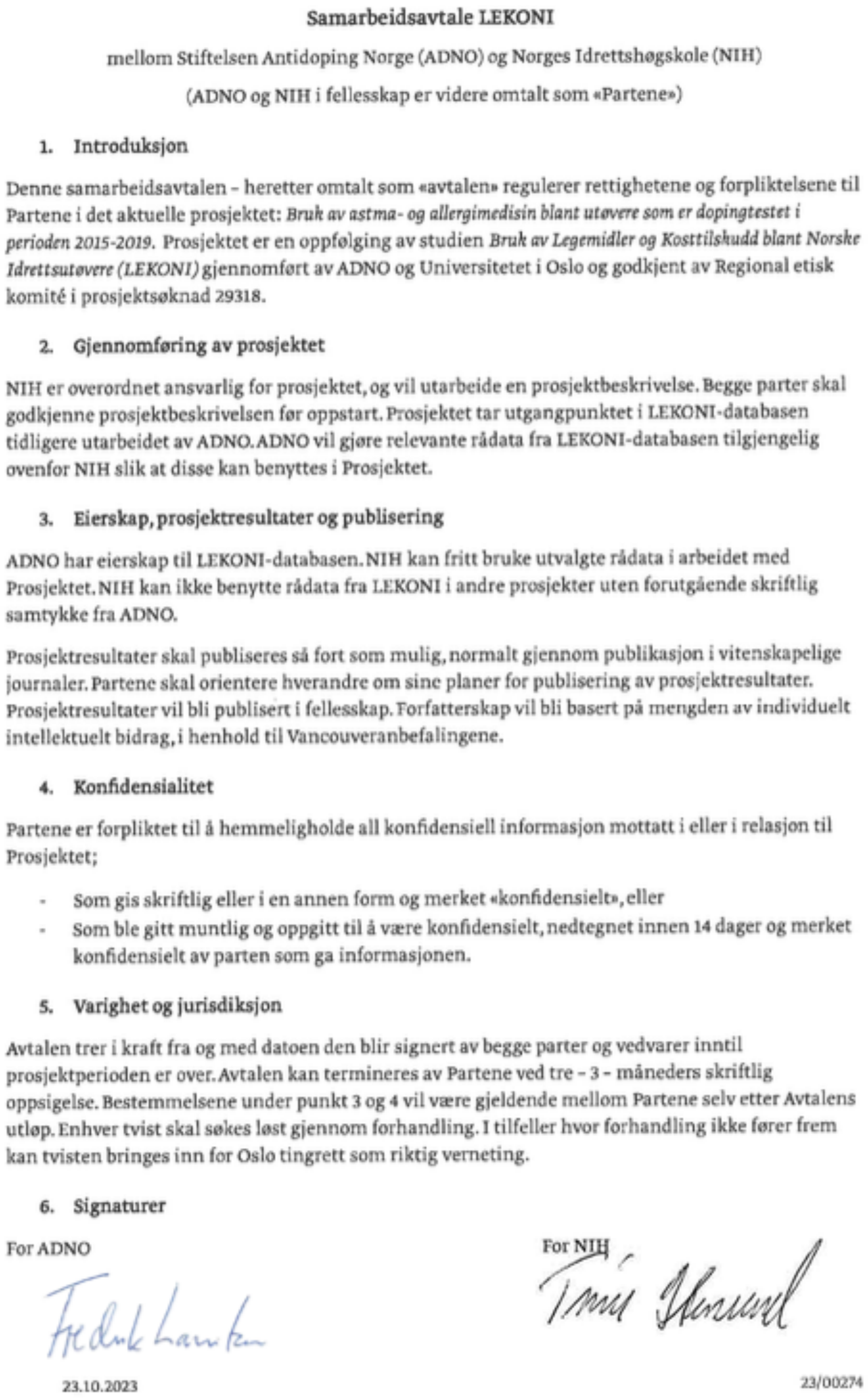


Can you check my spelling in this paragraph? Global Initiative for Asthma (GINA) defines asthma as ”a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms, such as wheeze, shortness of breath, chest tightness and cough, that vary over time and in intensity, together with variable expiratory airflow limitation.” (GINA, 2023, p. 22). In terms of lung physiology, asthma is typically characterized by reversible airflow obstruction, bronchial hyperresponsiveness (BHR) and distinct patterns of airway inflammation (GINA, 2023, p. 22). Definitions of asthma are generally consensus-based, recognizing a disease heterogeneity with clusters of demographics, clinical and/or pathophysiological characteristics often called “asthma phenotypes” (Kuruvilla et al., 2019).

Your paragraph is well-written, but here are a few minor suggestions for clarity and correctness:

1. Change “defines asthma as ”a” to “defines asthma as “a” (change the quotation marks to be consistent).
2. Consider changing “the history of respiratory symptoms” to “a history of respiratory symptoms” for improved readability.

4.10 Appendix 3: Collaboration agreement, the Norwegian School of Sports Sciences and Anti-Doping Norway



Samarbeidsavtale LEKONI

mellom Stiftelsen Antidoping Norge (ADNO) og Norges Idrettshøgskole (NIH)

(ADNO og NIH i fellesskap er videre omtalt som «Partene»)

1. Introduksjon

Denne samarbeidsavtalen – heretter omtalt som «avtalen» regulerer rettighetene og forpliktelsene til Partene i det aktuelle prosjektet: *Bruk av astma- og allergimedisin blant utøvere som er dopingtestet i perioden 2015-2019.* Prosjektet er en oppfølging av studien *Bruk av Legemidler og Kosttilskudd blant Norske Idrettsutøvere (LEKONI)* gjennomført av ADNO og Universitetet i Oslo og godkjent av Regional etisk komité i prosjektsøknad 29318.

2. Gjennomføring av prosjektet

NIH er overordnet ansvarlig for prosjektet, og vil utarbeide en prosjektbeskrivelse. Begge parter skal godkjenne prosjektbeskrivelsen før oppstart. Prosjektet tar utgangpunktet i LEKONI-databasen tidligere utarbeidet av ADNO. ADNO vil gjøre relevante rådata fra LEKONI-databasen tilgjengelig ovenfor NIH slik at disse kan benyttes i Prosjektet.

3. Eierskap, prosjektresultater og publisering

ADNO har eierskap til LEKONI-databasen. NIH kan fritt bruke utvalgte rådata i arbeidet med Prosjektet. NIH kan ikke benytte rådata fra LEKONI i andre prosjekter uten forutgående skriftlig samtykke fra ADNO.

Prosjektresultater skal publiseres så fort som mulig, normalt gjennom publikasjon i vitenskapelige journaler. Partene skal orientere hverandre om sine planer for publisering av prosjektresultater. Prosjektresultater vil bli publisert i fellesskap. Forfatterskap vil bli basert på mengden av individuelt intellektuelt bidrag, i henhold til Vancouveranbefalingene.

4. Konfidensialitet

Partene er forpliktet til å hemmeligholde all konfidensiell informasjon mottatt i eller i relasjon til Prosjektet;

- Som gis skriftlig eller i en annen form og merket «konfidensielt», eller
- Som ble gitt muntlig og oppgitt til å være konfidensielt, nedtegnet innen 14 dager og merket konfidensielt av parten som ga informasjonen.

5. Varighet og jurisdiksjon

Avtalen trer i kraft fra og med datoen den blir signert av begge parter og vedvarer inntil prosjektperioden er over. Avtalen kan termineres av Partene ved tre – 3 – måneders skriftlig oppsigelse. Bestemmelsene under punkt 3 og 4 vil være gjeldende mellom Partene selv etter Avtalens utløp. Enhver tvist skal søkes løst gjennom forhandling. I tilfeller hvor forhandling ikke fører frem kan tvisten bringes inn for Oslo tingrett som riktig verneting.

6. Signaturer

For ADNO	For NIH
23.10.2023	23/00274

4.11 Appendix 4: Approval by the Regional Committees for Medical and Health Research

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst C	Anders Strand		18.12.2019	29318
			Deres referanse:	

Astrid Gjelstad

Prosjektsøknad

29318 Bruk av legemidler og kosttilskudd hos norske idrettsutøvere (LEKONI)

Forskningsansvarlig: Universitetet i Oslo

Søker: Astrid Gjelstad

Vi viser til klage på vedtak for ovennevnte. Klagen ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst C) i møtet REK sør-øst C 05.12.2019 Komitemøte. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Søkers beskrivelse av formål:

Studien vil være en retrospektiv studie hvor trender i legemiddel- og kosttilskuddsbruk hos norske idrettsutøvere i en tidsperiode over fem år skal undersøkes. Bruk av legemidler og kosttilskudd kan i visse tilfeller betraktes som en uønsket del av trening og konkurranse i idretten. Det vil være av stor interesse å få bedre innsikt i bruk av legemidler og kosttilskudd blant idrettsutøvere, for slik å kunne iverksette tiltak der det er behov og eventuelt motvirke en medikalisering av toppidretten og treningsmiljøer for øvrig. Studien skal gjennomføres ved gjennomgang og registrering av relevante opplysninger gitt på dopingkontrollskjema i forbindelse med prøver innhentet fra Antidoping Norge i den aktuelle perioden. Når databasen er etablert vil denne danne utgangspunkt for å undersøke flere problemstillinger, blant annet om det er økt bruk av legemidler og kosttilskudd den aktuelle perioden, og om idrettsutøvere bruker flere legemidler enn befolkningen for øvrig.

Alle skriftlige henvendelser om saken må sendes via REK-portalen
Du finner informasjon om REK på våre hjemmesider rekportalen.no

Vurdering

Vurdering

Komiteen godkjente det angjeldende prosjektet på vilkår om innhenting av samtykke i vedtak av 23.09.2019. Komiteen skrev: «Prosjektet søker fritak fra kravet om innhenting av samtykke for bruk av utøverrapporterte opplysninger fra dopingkontrollskjema. Komiteen vurderte dette i to trinn. (1) På dopingkontrollskjema kan utøverne krysse av for at selve dopingprøven kan brukes i forskning. Dette reiser spørsmålet hvorvidt et slikt samtykke også er dekkende for bruk av selvrapporterte opplysninger fra dopingskjemaet. Komiteen mener at dette ikke er tilfelle da bruk av opplysninger ikke er nevnt i forbindelse med dette samtykket til forskning. Komiteen vurderte derfor (2) fritak fra samtykkekravet for bruk av selvrapporterte opplysninger fra dopingkontrollskjema i prosjektet. Dette reiser spørsmål om hva slags lovhjemmel eventuelt fritak skal vurderes opp mot i dette tilfellet. Det er her ikke snakk om opplysninger innsamlet i den ordinære helsetjenesten, jfr. helseforskningsloven §35. Det er heller ikke opplysninger samlet for forskningsformål, jfr. helseforskningsloven §15. Komiteen mener derfor at det ikke foreligger noen definert lovhjemmel for at REK skal kunne gi fritak fra innhenting av samtykke i dette tilfellet. Komiteen konkluderte derfor med at prosjektet må innhente samtykke fra aktuelle deltagere for bruk av selvrapporterte helseopplysninger i prosjektet, komiteen setter dette som vilkår for godkjenning.»

I klage av 11.11.2019, og i tilhørende supplerende informasjon av 14.11.2019, klargjør prosjektleder at opplysningene fra dopingkontrollskjemaet skal anonymiseres før det forskes på disse. Videre anfører søker at tilgangen på kontrollskjema, plottingen av opplysningene, og anonymiseringen av datafilen som skal danne grunnlag for analysene, har hjemmel i konsesjon fra Datatilsynet og er i tråd med World Anti Doping Code (WADC). Komiteen legger disse opplysningene til grunn, og mener at fritak fra samtykkekravet dermed ikke fremstår som påkrevet. Komiteen frafaller derfor vilkåret om innhenting av samtykke fra deltagere. Komiteen understreker i denne sammenheng at behandlingsansvarlig har ansvar for at det foreligger juridisk behandlingsgrunnlag for opplysningene etter personvernforordningen.

Komiteen opprettholder sin vurdering om at de som skal gjennomføre dataplottingen i prosjektet (farmasistudenter) fremstår som prosjektmedarbeidere i søknaden. Komiteen forutsetter derfor at prosjektet vurderer dette, og melder de inn som prosjektmedarbeidere til REK dersom de bidrar med selvstendig vitenskapelig arbeid eller hvis arbeidet vil inngå i deres utdanning.

I opprinnelig søknad og i klagen beskrives en rekke tiltak for å minimere muligheten for bakveisidentifisering av personer i datafilen, og dermed sikre at prosjektdataene er anonyme. Komiteen anser disse tiltakene som hensiktsmessige, men forutsetter likevel at prosjektet utviser spesiell aktsomhet i denne sammenheng, og at ytterligere tiltak implementeres dersom det avdekkes behov for dette. Personidentifiserbar informasjon skal ikke inkluderes i forskningsdatafilen eller fremkomme i publikasjoner fra prosjektet.

Omgjøringsvedtak

Vedtak: Godkjent

Komiteen frafaller vilkåret satt i vedtak av 23.09.2019 om innhenting av samtykke, omgjøringen ble gjort på bakgrunn av de nye opplysninger som fremkom i klagen.

Komiteens avgjørelse var enstemmig.

Britt Ingjerd Nesheim
professor dr. med.
leder REK sør-øst C

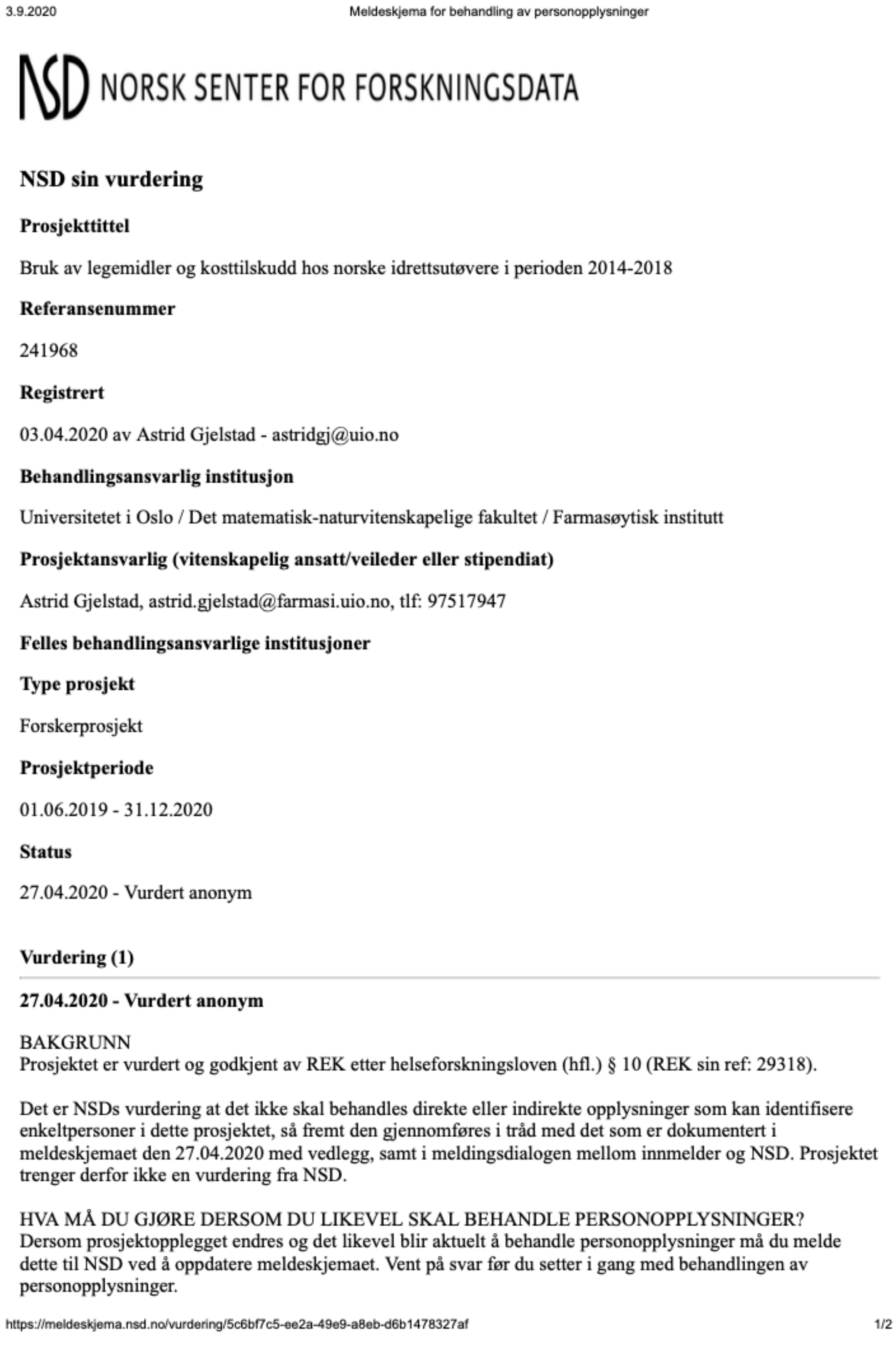
Anders Strand
Rådgiver

Dokumentet er elektronisk signert

Sluttmelding
Det skal sendes sluttmelding til REK sør-øst C på eget skjema senest seks måneder etter godkjenningsperioden er utløpt, jf. hfl. § 12.

Søknad om å foreta vesentlige endringer
Dersom man ønsker å foreta vesentlige endringer i forhold til formål, metode, tidsløp eller organisering, skal søknad sendes til den regionale komiteen for medisinsk og helsefaglig forskningsetikk som har gitt forhåndsgodkjenning. Søknaden skal beskrive hvilke endringer som ønskes foretatt og begrunnelsen for disse, jf. hfl. § 11.

4.12 Appendix 5: Approval by the Norwegian Center for Research Data [Norsk senter for forskningsdata]



NSD NORSK SENTER FOR FORSKNINGSDATA

NSD sin vurdering

Prosjekttittel

Bruk av legemidler og kosttilskudd hos norske idrettsutøvere i perioden 2014-2018

Referansenummer

241968

Registrert

03.04.2020 av Astrid Gjelstad - astridgj@uio.no

Behandlingsansvarlig institusjon

Universitetet i Oslo / Det matematisk-naturvitenskapelige fakultet / Farmasøytisk institutt

Prosjektansvarlig (vitenskapelig ansatt/veileder eller stipendiat)

Astrid Gjelstad, astrid.gjelstad@farmasi.uio.no, tlf: 97517947

Felles behandlingsansvarlige institusjoner

Type prosjekt

Forskerprosjekt

Prosjektperiode

01.06.2019 - 31.12.2020

Status

27.04.2020 - Vurdert anonym

Vurdering (1)

27.04.2020 - Vurdert anonym

BAKGRUNN
Prosjektet er vurdert og godkjent av REK etter helseforskningsloven (hfl.) § 10 (REK sin ref: 29318).

Det er NSDs vurdering at det ikke skal behandles direkte eller indirekte opplysninger som kan identifisere enkeltpersoner i dette prosjektet, så fremt den gjennomføres i tråd med det som er dokumentert i meldeskjemaet den 27.04.2020 med vedlegg, samt i meldingsdialogen mellom innmelder og NSD. Prosjektet trenger derfor ikke en vurdering fra NSD.

HVA MÅ DU GJØRE DERSOM DU LIKEVEL SKAL BEHANDLE PERSONOPPLYSNINGER?
Dersom prosjektopplegget endres og det likevel blir aktuelt å behandle personopplysninger må du melde dette til NSD ved å oppdatere meldeskjemaet. Vent på svar før du setter i gang med behandlingen av personopplysninger.

VI AVSLUTTER OPPFØLGING AV PROSJEKTET
Siden prosjektet ikke behandler personopplysninger avslutter vi all videre oppfølging.

Lykke til med prosjektet!

Kontaktperson hos NSD: Karin Lillevold

Tlf. Personverntjenester: 55 58 21 17 (tast 1)