ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ ΑΘΗΝΩΝ
ΠΑΘΟΛΟΓΙΚΟΣ ΤΟΜΕΑΣ

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ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ». ΔΙΕΥΘΥΝΤΡΙΑ: ΑΝΤΩΝΙΑ ΚΟΥΤΣΟΥΚΟΥ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

PHYSICAL ACTIVITY IN DAILY LIFE IN PATIENTS WITH ASTHMA AND THE EFFECT OF ANTI-INTERLEUKIN-5 THERAPY.

ΜΑΡΙΟΣ ΠΑΝΑΓΙΩΤΟΥ

ΠΝΕΥΜΟΝΟΛΟΓΟΣ ΙΑΤΡΟΣ

ΑΘΗΝΑ 2023

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ΑΘΗΝΑ 2023

Ημερομηνία αιτήσεως υποψηφίου: 23/2/2018

Ημερομηνία ορισμού τριμελούς συμβουλευτικής επιτροπής: 29/6/2018

Μέλη τριμελούς συμβουλευτικής επιτροπής:

1. Νικολέττα Ροβίνα, *Αναπληρώτρια Καθηγήτρια Πνευμονολογίας/Εντατικής Θεραπείας, ΕΚΠΑ.*
2. Νικόλαος Κουλούρης, *Καθηγητής Πνευμονολογίας, ΕΚΠΑ.*
3. Παρασκευή Κατσαούνου, *Αναπληρώτρια Καθηγήτρια Πνευμονολογίας, ΕΚΠΑ.*

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Πρόεδρος Ιατρικής Σχολής: Καθηγητής Γεράσιμος Δ. Σιάσος

Μέλη επταμελούς εξεταστικής επιτροπής:

1. Νικολέττα Ροβίνα, *Αναπληρώτρια Καθηγήτρια Πνευμονολογίας/Εντατικής Θεραπείας, Ιατρική Σχολή, ΕΚΠΑ.*
2. Νικόλαος Κουλούρης, *Καθηγητής Πνευμονολογίας, Ιατρική Σχολή, ΕΚΠΑ.*
3. Παρασκευή Κατσαούνου, *Αναπληρώτρια Καθηγήτρια Πνευμονολογίας, Ιατρική Σχολή, ΕΚΠΑ.*
4. Πέτρος Μπακάκος, *Καθηγητής Πνευμονολογίας, Ιατρική Σχολή, ΕΚΠΑ.*
5. Κωνσταντίνος Κωστίκας, *Καθηγητής Πνευμονολογίας, Τμήμα Ιατρικής, Πανεπιστήμιο Ιωαννίνων.*
6. Πασχάλης Στειρόπουλος, *Αναπληρωτής Καθηγητής Πνευμονολογίας, Τμήμα Ιατρικής, Δημοκρίτειο Πανεπιστήμιο Θράκης*.
7. Ανδριάνα Παπαϊωάννου, *Επίκουρη Καθηγήτρια Πνευμονολογίας, Ιατρική Σχολή, ΕΚΠΑ.*

Βαθμός Διατριβής: ΑΡΙΣΤΑ

ΣΕΛΙΔΑ

ΠΡΟΣΩΠΙΚΟ ΣΗΜΕΙΩΜΑ

Η παρούσα διδακτορική διατριβή συνιστά το αποτέλεσμα μιας ειλικρινούς προσπάθειας τεσσάρων ετών εκ μέρους των ερευνητών και των συμμετεχόντων ασθενών με στόχο την μελέτη και ανάδειξη της σημασίας της φυσικής δραστηριότητας στην καθημερινή ζωή των ασθενών με άσθμα και της συνεισφοράς των νεότερων θεραπευτικών προσεγγίσεων στον τομέα αυτό. Τα ευρήματα της συλλογικής αυτής προσπάθειας έλαβαν επαρκούς αναγνώρισης μέσα από παρουσιάσεις σε διεθνή επιστημονικά συνέδρια και παρουσιάσεις σε έγκυρα ιατρικά περιοδικά.

Σε προσωπικό επίπεδο, η παρούσα διδακτορική διατριβή αποτελεί επιπλέον το επιστέγασμα και τη μετουσίωση σε ένα τιμητικό ακαδημαϊκό τίτλο μιας αποδοτικής ερευνητικής δραστηριότητας από τα πρωιμότερα βήματα της ιατρικής μου πορείας έως και σήμερα. Σταθερό και βασικότερο κίνητρο μου στην διαδρομή αυτή αποτέλεσε η επιθυμία για συνεισφορά στην ιατρική γνώση και βελτίωση της ιατρικής φροντίδας για τον ασθενή. Επιπρόσθετη ώθηση έπαιρνα πάντα από την ευχαρίστηση που απορρέει από την ενασχόληση με την επιστημονική έρευνα και την ανακάλυψη της νέας γνώσης.

Η πραγμάτωση της παρούσας εργασίας όπως και οποιασδήποτε άλλης επαγγελματικής μου δραστηριότητας, δε θα μπορούσε να καταστεί εφικτή χωρίς την επιστημονική, ηθική και πρακτική αρωγή, πολύτιμες εμπειρίες, γνώσεις, ικανότητες και δεξιότητες τις οποίες αποκόμισα και συνεχίζω να αποκομίζω μέσα από την επαγγελματική και προσωπική, ανθρώπινη επαφή. Για τον λόγο αυτό επιθυμώ να εκφράσω τον απεριόριστο σεβασμό μου, ευχαριστίες και ευγνωμοσύνη, στην επιβλέπουσα μου Νικολέττα Ροβίνα και σε όλους εσάς τους συναδέλφους ιατρούς και δασκάλους, επιστημονικούς συνεργάτες και ασθενείς τους οποίους είχα ποτέ την ευκαιρία να γνωρίσω, να συνεργαστώ και να μάθω από εσάς. Εκφράζω επίσης την ευγνωμοσύνη μου και ένα μεγάλο ευχαριστώ σε εσάς, γονείς μου Πρόδρομε και Ξένια, Μάριε, Αντώνη, Εβίτα, Χρίστο, Γιώργο, Φρόσω, Adam και άλλοι πολύτιμοι και αγαπημένοι που μαζί σας μπόρεσα να γίνω και να συνεχίσω να γίνομαι καλύτερος άνθρωπος!

Μάριος Παναγιώτου

ΒΙΟΓΡΑΦΙΚΟ ΣΗΜΕΙΩΜΑ

Δρ. ΜΑΡΙΟΣ ΠΑΝΑΓΙΩΤΟΥ

ΠΝΕΥΜΟΝΟΛΟΓΟΣ - ΦΥΜΑΤΙΟΛΟΓΟΣ
MD, PhD, MRCP(UK), ERS Diplomate/Fellow

mpanagiotou@med.uoa.gr
mariopanag@gmail.com

ΙΑΤΡΙΚΟΙ ΤΙΤΛΟΙ & ΔΙΑΚΡΙΣΕΙΣ

2023	**Διδάκτορας Ιατρικής Σχολής** **Εθνικού και Καποδιστριακού Πανεπιστημίου Αθηνών** Βαθμός διδακτορικής διατριβής: Άριστα
2015	**Membership of the Royal Colleges of Physicians of the United Kingdom** (MRCP(UK))
2014	**Long-Term Research Fellowship in Pulmonary Arterial Hypertension** European Respiratory Society
2014	**HERMES Diploma in Adult Respiratory Medicine** European Respiratory Society.
2014	**Τίτλος Ιατρικής Ειδικότητας Πνευμονολογίας – Φυματιολογίας** Ελληνικό Υπουργείο Υγείας
2006	**Πτυχίο Ιατρικής** Ιατρική Σχολή Πανεπιστημίου Πάτρας Εγγραφή: 2000. Βαθμός πτυχίου: 7.16/10
2000	**Υποτροφίες Ιατρικών Σπουδών** Ίδρυμα Κρατικών Υποτροφιών Κύπρου & Παγκύπριο Λύκειο Λευκωσίας Κύπρου

ΕΠΙΣΤΗΜΟΝΙΚΕΣ ΔΡΑΣΤΗΡΙΟΤΗΤΕΣ/ΕΓΓΡΑΦΕΣ

Invited Member of the European Respiratory Society College of Experts, από το 2014

Member of the European Respiratory Society: 302304

Μέλος Ελληνικής Πνευμονολογικής Εταιρείας

Μέλος Ιατρικού Συλλόγου Αθηνών: 079992

ΕΠΑΓΓΕΛΜΑΤΙΚΗ ΕΜΠΕΙΡΙΑ

Σεπ 2016 – σήμερα	**Ιδιώτης Πνευμονολόγος Ιατρός** Πνευμονολογικό Ιατρείο AthensLung, Αθήνα
Ιουν 2108 – Φεβ 2023	**Υποψήφιος Διδάκτορας** Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών 1η Πανεπιστημιακή Πνευμονολογική Κλινική, ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ» Τίτλος διδακτορικής διατριβής: Physical activity in daily life in patients with asthma and the effect of anti-interleukin-5 therapy.
Απρ 2017 – Ιουλ 2018	**Ιατρικός Διευθυντής Παθολογικού Ιατρείου** «Γιατροί του Κόσμου – Ελλάδας», ανθρωπιστική, μη-κυβερνητική οργάνωση
Ιαν 2016 – Σεπ 2016	**Senior Clinical Fellow in Respiratory Medicine** Queen Elizabeth University Hospital, Glasgow, UK.
Σεπ 2014 – Δεκ 2015	**European Respiratory Society Research Fellow in Pulmonary Arterial Hypertension** Scottish Pulmonary Vascular Unit, Golden Jubilee National Hospital, Glasgow, UK.
Απρ 2011– Ιουν 2014	**Ειδικευόμενος Πνευμονολόγος Ιατρός** 2η Πνευμονολογική Κλινική, Σισμανόγλειο Γενικό Νοσοκομείο Αθηνών & Πανεπιστημιακή Μονάδα Εντατικής Θεραπείας, ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ».
Μαρ 2007 – Δεκ 2011	**Ειδικευόμενος Ιατρός στην Πνευμονολογία, Καρδιολογία, Ενδοκρινολογία, Γαστρεντερολογία, Επείγουσα Ιατρική, Γηριατρική, Μονάδα Αγγειακών Εγκεφαλικών Νοσημάτων & Αποκατάστασης και Πρωτοβάθμια Υγεία (Foundation and Core Medical Trainee)** Queen Alexandra Hospital, NHS UK. Kettering General Hospital, NHS UK. Diana Princess of Wales Hospital, NHS UK.
Σεπ 2006 – Μαρ 2007	**Honorary Clinical Attaché in Emergency Medicine** University College Hospital, London, UK Χρηματοδότηση από Πανεπιστήμιο Πατρών και το Ευρωπαϊκό πρόγραμμα επαγγελματικής εκπαίδευσης και κατάρτισης “Leonardo Da Vinci”.

ΕΠΙΣΤΗΜΟΝΙΚΕΣ ΔΗΜΟΣΙΕΥΣΕΙΣ

1ος Συγγραφέας: **15** | Citations: **270** | h-index **8** (Google Scholar 02/2023)

1. M. Panagiotou, et al. Daily physical activity in asthma and the effect of mepolizumab therapy. *J Pers Med 2022; 12, 1692.*
2. Panagiotou M, et al. Physical activity: a missing link in asthma care. *J Clin Med 2020; 9, 706.*
3. Panagiotou M, et al. Daily physical activity in patients with severe eosinophilic asthma and the effect of anti-IL-5 therapy. *EMJ Respir 2018; 6, 74-77.*
4. Panagiotou M, et al. A study of clinical and physiological relations of daily physical activity in precapillary pulmonary hypertension.
   J Appl Physiol (1985) 2017; jap.00986.2016.
5. Panagiotou M, et al. Validation of impedance cardiography in pulmonary arterial hypertension. *Clin Physiol Funct Imaging 2018; 38, 254-260.*
6. Panagiotou M, et al. Pulmonary vascular and cardiac impairment in interstitial lung disease. *Eur Respir Rev 2017; 26, 160053.*
7. Panagiotou M, et al. Dynamic near-infrared spectroscopy assessment as an important tool to explore pulmonary arterial hypertension pathophysiology.
   Eur Respir J 2017; 49, 1602161.
8. Panagiotou M, et al. Near infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension.
   Eur Respir J 2016; 48, 1224-1227.
9. Panagiotou M, et al. 25-hydroxyvitamin D in malignant pleural disease: A prospective cohort study. *Clin Respir J 2018; 12, 467-473.*
10. Panagiotou M, et al. Respiratory and limb muscle function in interstitial lung disease. *Chron Respir Dis 2016; 13, 162-172.*
11. Panagiotou M, et al. Respiratory and limb muscle dysfunction in pulmonary arterial hypertension. A role for exercise training? *Pulm Circ 2015; 5, 424-434.*
12. Panagiotou M. et al. The epidemiology of nontuberculous mycobacteria. Data from a General Hospital of Athens, Greece 2007-2013. *Pulm Med 2014; 2014, 894976.*
13. Panagiotou M, et al. Immune response to mycobacterial infection: lessons from flow cytometry. *Clin Dev Immunol 2013; 2013, 464039.*

14. Panagiotou M, et al. Exercise limitation in COPD. *Pneumon 2013; 26, 245-256*.

15. Panagiotou M, et al. A Case of tracheal hamartoma resected with loop electrocautery. *Case Rep Pulmonol 2013; 2013, 568590*.

ΕΠΙΣΤΗΜΟΝΙΚΕΣ ΟΜΙΛΙΕΣ & ΔΙΔΑΣΚΑΛΙΑ

1. European Respiratory Society (ERS) Congress, Παρίσι 2018 & Μαδρίτη 2019. Late Breaking Abstracts: Daily physical activity in patients with severe eosinophilic asthma and the effect of anti-IL-5 therapy: **Προφορικές Ανακοινώσεις**

2. 6th International Workshop on Lung Health, Νίκαια, Γαλλία 2019. Daily physical activity in patients with severe eosinophilic asthma and the effect of anti-IL-5 therapy: **Αναρτημένη Ανακοίνωση**

3. ERS course on Pulmonary Rehabilitation, Αθήνα 2017: **Διδάσκων**

4. Πρόγραμμα Μεταπτυχιακών Σπουδών «Καρδιοπνευμονική Αποκατάσταση και Αποκατάσταση Πασχόντων ΜΕΘ», Ιατρική Σχολή ΕΚΠΑ, 2017-18: **Διδάσκων**

5. Πρόγραμμα Μεταπτυχιακών Σπουδών «Άσκηση, Εργοσπιρομετρία και Αποκατάσταση», Ιατρική Σχολή Πανεπιστημίου Θεσσαλίας, 2016-17: **Διδάσκων**

6. 7η Ημερίδα στην Καρδιακή Ανεπάρκεια, 1η Πανεπιστημιακή Καρδιολογική Κλινική, Ιπποκράτειο Νοσοκομείο Αθηνών, 2016: **Ομιλητής**

7. UK Pulmonary Hypertension Physicians Research Forum, Λονδίνο 2015: **Ομιλητής**

8. ERS Congress, Άμστερνταμ 2015. Physiological and clinical correlations of daily physical activity in patients with precapillary pulmonary hypertension: **Αναρτημένη Ανακοίνωση**

9. ERS Congress, Άμστερνταμ 2015. The value of near infrared spectroscopy in the investigation of peripheral muscle oxygen availability in pulmonary arterial hypertension: **Αναρτημένη Ανακοίνωση**

10. Seminar on novel approaches for assessing the distribution of regional muscle blood flow & metabolic rate during exercise: Institute of Clinical Exercise & Health Sciences, University of the West of Scotland, UK 2015: **Ομιλητής**

11. ERS Congress, Βαρκελώνη 2013 και ACCP World Congress 2014, Μαδρίτη. Vitamin D in malignant pleural disease: **Αναρτημένες Ανακοινώσεις**

12. Πρόγραμμα Μεταπτυχιακών Σπουδών «Άσκηση και Υγεία», Τμήμα Επιστήμης Φυσικής Αγωγής και Αθλητισμού Πανεπιστημίου Θεσσαλίας, 2013-14: **Διδάσκων**

13. ACCP CHEST Congress, Ατλάντα 2012. Factors determining the duration of hospital stay in acute exacerbation of COPD: **Αναρτημένη Ανακοίνωση**

ΣΥΜΜΕΤΟΧΕΣ ΣΕ ΕΠΙΣΤΗΜΟΝΙΚΕΣ ΔΡΑΣΤΗΡΙΟΤΗΤΕΣ

- ERS Pulmonary Hypertension and Pulmonary Vascular Disease courses, Lausanne, 2014 & 2018.
- ERS Research Seminar: Use of biologics in adults/adolescents with severe refractory asthma and setting a future research agenda, London 2018.
- ERS International Congress 2015, 2016, 2017, 2018, 2019.
- Advanced Life Support (ALS) course, European Resuscitation Council 2015.
- ERS Lung Science Conference, Lisbon 2015.
- ERS Smoking Cessation seminar, Athens 2012.
- ERS course on Interventional Pulmonology & Thoracic Endoscopy, Athens 2012.
- Ill Medical Patients' Acute Care & Treatment (IMPACT) course, UK 2009.
- NHS Lead or be Led course, UK 2009.
- British Thoracic Society (BTS) Winter meeting, UK 2009.
- BTS Non-Invasive Ventilation (acute & chronic) course, UK 2009.
- Effective Teaching Skills course, The Royal College of Physicians of the UK, 2009.
- Research Methods & Critical Appraisal course, The Royal Society of Medicine, UK 2009.
- Ultrasound-Guided Central Line Insertion course, UK 2008.
- BMJ Masterclass in Respiratory Medicine, UK 2008.
- MDU Medical Ethics & Law workshop, UK 2007.
- Yorkshire Chest Imaging course, UK 2007.

A. GENERAL PART

(LITERATURE REVIEW)

1. INTRODUCTION

Asthma is the commonest respiratory disease and one of unceasingly increasing prevalence and burden. As such, asthma has attracted a major share of scientific interest and clinical attention. For the various clinical and pathophysiological aspects of asthma having been extensively investigated, the specific association between asthma and physical activity in daily life remains underappreciated and insufficiently explored. Asthma impacts adversely on physical activity; likewise, poor physical activity may lead to worse asthma outcomes. This concise literature review presents the current recommendations for physical activity, discusses the available evidence on physical activity in asthma and examines the causes of low physical activity in adult asthmatic patients. It also reviews the effect of physical activity in daily life and exercise training on the pathology and clinical outcomes of asthma. Finally, it summarizes the evidence on interventions targeting physical activity in asthma.

2. PHYSICAL ACTIVITY: NOMENCLATURE

Physical activity is comprised of bodily movements produced by the skeletal muscles that result in an increased metabolic rate over that of resting energy expenditure [1]. Physical activity in daily life (PADL) encompasses household, occupational, transportation, conditioning, athletics, sports or other activities in the context of daily, family, and community activities. As such, PADL satisfies the core requirement of a meaningful clinical trial endpoint defined to be a direct measure of how a patient feels, functions or survives where function refers to the ability to carry out normal daily activities [2], and is becoming of increasing research and clinical interest. Definite evidence confirms that physical activity confers a dose-dependent benefit for all-cause mortality, cardiovascular disease mortality, incident hypertension, incident type 2 diabetes, incident site-specific cancers, mental health (anxiety and depression), cognitive health, sleep and obesity [3-5], but also for health-related quality of life in both health [6, 7] and disease [9,10], across all ages [8].

Physical activity can be described by dimensions of intensity, frequency, duration, mode and context. For the purpose of improving health outcomes, the intensity, frequency and duration of physical activity must be collectively considered [9]. Intensity refers to the rate at which work is being performed or the magnitude of the effort required to perform an activity or exercise and it can be expressed either in absolute or relative terms [10]. For aerobic physical activity, measured or estimated measures of absolute intensity include caloric expenditure (kilocalories(kcal)·min^{-1}), absolute oxygen uptake (ml·min^{-1}), metabolic equivalents, or physiological response to the intensity (e.g., heart rate). For resistance activity,

intensity is frequently expressed as the amount of weight lifted or moved. These absolute measures can result in misclassification of the intensity of physical activity (e.g., moderate, vigorous) because they do not consider individual factors such as age, body weight, sex, and fitness level accounting for the physiological capacity of the individual [7]. The misclassification error is greater when using estimated rather than directly measured absolute energy expenditure, and under free-living compared with laboratory conditions, especially for older and deconditioned persons [11].

Relative intensity takes into account or adjusts to an individual's maximal exercise capacity. For aerobic physical activity, relative intensity is expressed as a percentage of maximal oxygen uptake ($V\dot{O}_{2max}$) or $V\dot{O}_{2max}$ reserve, a percentage of an individual's measured or estimated maximum heart rate, or heart rate reserve. It also can be expressed as an index of how hard an individual feels during performing a certain physical activity (e.g., on a 0–10 scale) [10].

Most epidemiologic and several laboratory studies on physical activity classify the intensity of physical activity using estimates of absolute energy expenditure in terms of metabolic equivalents (METs). The MET concept represents a simple, practical, and easily understood procedure for expressing the energy expenditure of physical activities as a multiple of the resting metabolic rate. One metabolic equivalent is defined as the amount of oxygen consumed while sitting at rest, assumed to be equal to 3.5 ml $O_2.kg^{-1}.min^{-1}$, which corresponds to an energy expenditure of 1 $kcal.kg^{-1}.hour^{-1}$. The energy cost of an activity in METs can be therefore determined by dividing the relative oxygen cost of the activity (ml $O_2.kg^{-1}.min^{-1}$) by 3.5 [12]. Physical activity may then be classified by its intensity,

using the MET value as a reference. For people of all ages weighing ~68-91 kg, physical activity is considered sedentary when requiring <1.5 METs, light when requiring 1.5-2.9 METs, moderate when requiring 3-5.9 METs and vigorous when requiring ≥6 METs [3, 11]. Table 1 presents the MET equivalents of common physical activities classified as light, moderate or vigorous intensity; for a comprehensive listing of MET values see tabulation by Ainsworth and colleagues [13]. The volume of physical activity can be expressed in METs per the duration that the activity was performed (e.g., in minutes), by the MET minute (MET·min) index. The MET·min index therefore quantifies the rate of energy expenditure for the duration an activity is performed, standardized for body size and resting metabolism.

Light <3.0 METs	Moderate 3.0 – 6.0 METs	Vigorous >6.0 METs
Walking	Walking	Walking, jogging & running
Walking slowly around home, store or office = 2.0*	Walking 3.0 mph = 3.3*	Walking at very very brisk pace (4.5 mph) = 6.3*
	Walking at very brisk pace (4 mph) = 5.0*	Walking/hiking at moderate pace and grade with no or light pack (<10 lb) = 7.0
		Hiking at steep grades and pack 10–42 lb = 7.5–9.0
		Jogging at 5 mph = 8.0*
		Jogging at 6 mph = 10.0*
		Running at 7 mph = 11.5*
Household & occupation		
Sitting — using computer work at desk using light hand tools = 1.5	Cleaning — heavy: washing windows, car, clean garage = 3.0	Shoveling sand, coal, etc. = 7.0
Standing performing light work such as making bed, washing dishes, ironing, preparing food or store clerk = 2.0–2.5	Sweeping floors or carpet, vacuuming, mopping = 3.0–3.5	Carrying heavy loads such as bricks = 7.5
	Carpentry — general = 3.6	Heavy farming such as bailing hay = 8.0
	Carrying & stacking wood = 5.5	Shoveling, digging ditches = 8.5
	Mowing lawn — walk power mower = 5.5	
Leisure time & sports		
Arts & crafts, playing cards = 1.5	Badminton — recreational = 4.5	Basketball game = 8.0
Billiards = 2.5	Basketball — shooting around = 4.5	Bicycling — on flat: moderate effort (12–14 mph) = 8.0; fast (14–16 mph) = 10
Boating — power = 2.5	Bicycling — on flat: light effort (10–12 mph) = 6.0	Skiing cross country — slow (2.5 mph = 7.0; fast (5.0–7.9 mph) = 9.0
Croquet = 2.5	Dancing — ballroom slow = 3.0; ballroom fast = 4.5	Soccer — casual = 7.0; competitive = 10.0
Darts = 2.5	Fishing from river bank & walking = 4.0	Swimming — moderate/hard = 8–11†
Fishing — sitting = 2.5	Golf — walking pulling clubs = 4.3	Tennis singles = 8.0
Playing most musical instruments = 2.0–2.5	Sailing boat, wind surfing = 3.0	Volleyball — competitive at gym or beach = 8.0
	Swimming leisurely = 6.0†	
	Table tennis = 4.0	
	Tennis doubles = 5.0	
	Volleyball — noncompetitive = 3.0–4.0	

Table 1: MET equivalents of common physical activities classified as light, moderate or vigorous intensity (Adapted from [14]).

Despite the widespread acceptance that the MET concept has gained, it comes with limitations inherent in its assumption which may result in misclassification of the intensity of physical activity. For example, the accepted 1-MET value of 3.5 ml $O_2.kg^{-1}.min^{-1}$ overestimated the actual resting $\dot{V}O_2$ by 35% and the 1-MET value of 1 $kcal.kg^{-1}.hour^{-1}$ overestimated the resting energy expenditure by 20%, unless corrected for the measured or predicted resting metabolic rate (a product of the body composition, body mass index, age and gender) [15]. Furthermore, older adults have been shown to have 1-MET values 31% lower than 3.5 ml $O_2.kg^{-1}.min^{-1}$ [16]. This means, for example, that an older person working at 6 METs may be exercising at a vigorous to maximal intensity, while a younger person working at the same absolute intensity will be exercising moderately [11]. Accordingly, age-specific MET thresholds have been proposed for the assessment of mortality risk [17]. Also, higher thresholds for moderate (4.9 METs) and vigorous (6.8 METs) physical activity have been reported to have improved specificity compared to the currently recommended thresholds [18].

3. PHYSICAL ACTIVITY: RECOMMENDATIONS

In order to improve cardiorespiratory and muscular fitness and gain benefit in all-cause and cardiovascular disease mortality, incident cancer and diabetes and mental health the World Health Organization (WHO) advices that adults should engage in at least 150-300 minutes of moderate-intensity aerobic physical activity throughout the week or do at least 75-150 minutes of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate-and vigorous-intensity activity (MVPA; ≥3 METs) [3]. Preferably, aerobic activity should be spread evenly over 4 to 5 days a week, or every day. When combining moderate and vigorous intensity activity to meet the current recommendation, the minimum goal should be in the range of 600 to 1,200 MET·min per week (average 100 to 120 MET·min per day). These values are calculated by assigning an average of 4 METs to 150-300 minutes spent in moderate intensity per week (4 × 150 = 600 and 4 × 300 = 1,200). The same values are calculated by assigning an average of 8 METs to 75-150 minutes spent in vigorous activities (8 × 75 = 600 and 8 × 150 = 1,200) [19]. These recommendations are relevant to all healthy adults aged 18 and older (including aged 65 and older), regardless of gender, race, cultural background or socioeconomic status and are relevant for people of all abilities. They also apply to individuals with chronic noncommunicable medical conditions not related to mobility, including asthma and are reproduced in several national guidelines [11, 20-22].

The WHO guidelines also advise adults to perform muscle-strengthening activities at moderate or greater intensity that involve all major muscle groups on 2 or more days a week, as these provide additional health benefits [3]. In older adults

(65 years and above), physical activity also helps prevent falls and falls-related injuries and declines in bone health and functional ability. Therefore, as part of their weekly physical activity, older adults should do varied multicomponent physical activity that emphasizes functional balance and strength training at moderate or greater intensity on 3 or more days a week [3].

The above recommendations refer to the minimal required amount of activity in order to achieve substantial benefits over and above the routine light-intensity activities of daily living. For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to >300 minutes per week or engage in >150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of MVPA [3]. Any increase in duration or frequency of MVPA associated with a progressively lower risk of all-cause mortality [4, 23, 24] but strong evidence suggests that total physical activity needs to be several times higher than the recommended minimum level of 600 MET·min per week to achieve significant health benefits such as reducing the risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events [25]. Interestingly, most health gains were shown to occur at relatively lower levels of activity (up to 3,000–4,000 MET·min per week), with diminishing returns at higher levels of activity [25].

In a United States (U.S) national cohort study of 403,681 adults, both the recommended levels of moderate physical activity (MPA) and vigorous physical activity (VPA) showed similar associations for all-cause mortality and cardiovascular disease but VPA showed a stronger inverse association with cancer mortality compared with MPA [26]. Also, among participants performing any MVPA,

a higher proportion of VPA to total physical activity was associated with lower all-cause mortality. The inverse association between proportion of VPA to total physical activity and all-cause mortality was consistent across sociodemographic characteristics, lifestyle risk factors, and chronic conditions at baseline [26], showing that VPA is an indispensable aspect of PADL.

Previous guidelines advised that only activities performed in bouts of 10 minutes or more (not interrupted for more than 1 min) could be counted towards the recommended goals [27]. However, few activities in contemporary life are conducted routinely at a moderate intensity for at least 10 minutes in duration without interruptions. Furthermore, updated evidence from population studies shows that physical activity of any bout duration is associated in a dose-dependent fashion with improved health outcomes, including reduction in all-cause mortality [23, 28, 29]. In plain words, it is now widely accepted that there is no minimum amount of physical activity required to achieve health benefits; physical activity of any bout duration, accumulated over the day and week will also provide benefits. Specific targets below the recommended levels can be effective as a behavioral goal for people starting from low levels of activity (including disabled adults and those with long-term conditions), and as a step on the journey towards meeting the recommended levels [21].

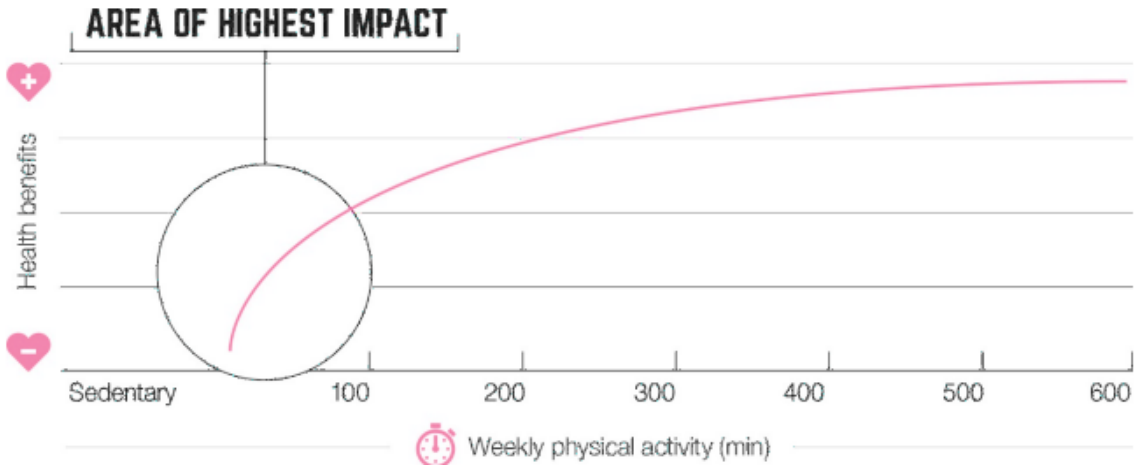


Figure 1: Dose-response curve of physical activity and health benefits (From [21]).

The baseline number of steps per day in general populations varies across studies but the typical amount is about 5,000 steps a day, although this may actually be too high for some older adults and/or special populations [20, 30]. For estimating step count over a day, all types of activities during the day may be counted such as taking stairs, doing errands by walking, or breaking up sedentary behavior by standing and moving during the work day [20].

Classification of physical activity by steps has been suggested [31] (Figure 2) but there are currently no evidence-based public health guidelines for the daily step count. Although the goal of 10,000 steps per day is widely promoted as being optimal for general health, it is not based on evidence, but instead originates from an old marketing campaign in Japan [32]. Expert committees from the WHO 2020 Physical Activity Guidelines and US 2018 Physical Activity Guidelines identified a gap in research on the dose–response association between volume and intensity of physical activity and health outcomes, including physical activity measured by step volume and rate. However, recent robust evidence from the largest meta-analysis of

15 studies (sample 47,471 adults) showed that taking more steps per day was associated with a progressively lower risk of all-cause mortality, up to a level that varied by age [5]. Specifically, taking more steps per day was associated with progressively lower mortality risk, with the risk plateauing for older adults (aged ≥60 years) at approximately 6,000–8,000 steps per day and for younger adults (aged <60 years) at approximately 8,000–10,000 steps per day [5]. Therefore, mortality benefits, particularly for older adults, can occur at levels less than the popular reference value of 10,000 steps per day.

The curvilinear association between steps per day and all-cause mortality (Figure 3) and the 50–60% lower risk in the higher steps per day quartiles than in the lowest steps per day quartile is similar to the association and risks observed for time spent doing MVPA and mortality, and study-level publications on steps and mortality [5]. The steep early slope of the dose–response curve suggests that increasing steps might be beneficial in terms of reducing risk of mortality, particularly among individuals who have lower step volumes. Eventually, a plateau in risk reduction is observed at higher step count, which varies by age group [5]. Notably, it is estimated that 80 percent of daily steps among less active people are light intensity [20] but evidence remains inconclusive when determining if step intensity has additional mortality benefits beyond that associated with total steps [5].

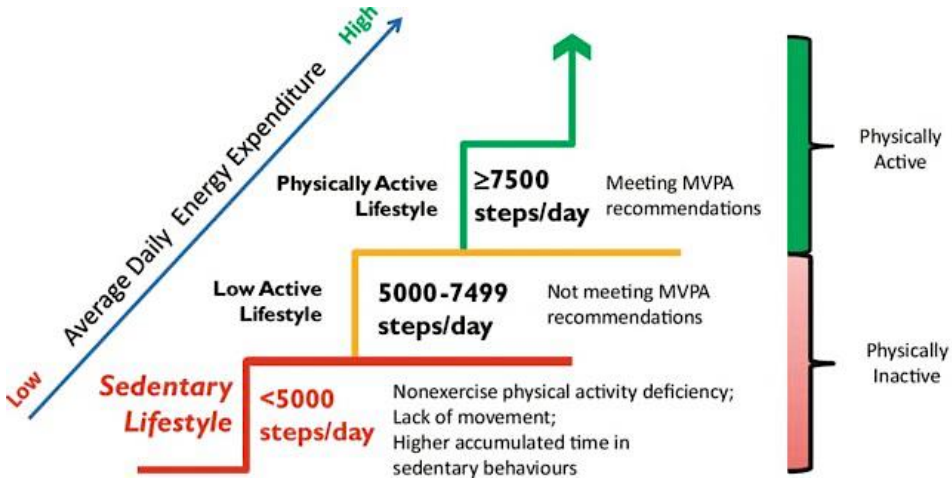


Figure 3: Step-defined activity lifestyle index for adults. MVPA, moderate-to-vigorous physical activity (From [31]).

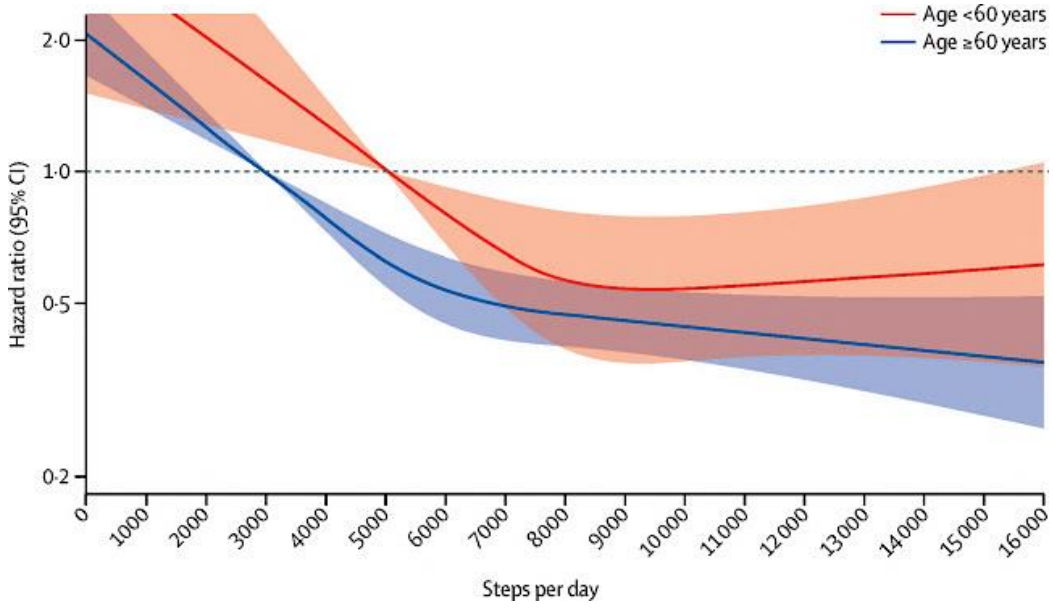


Figure 3: Dose-response association between steps per day and all-cause mortality, by age group. Thick lines indicate hazard ratio estimates, with shaded areas showing 95% CIs. Reference set at the median of the medians in the lowest quartile group (age ≥60 years = 3000 steps per day and <60 years = 5000 steps per day). Model is adjusted for age, accelerometer wear time, race and ethnicity (if applicable), sex (if applicable), education or income, body-mass index, and study-specific variables for lifestyle, chronic conditions or risk factors, and general health status. (From [5])

Translated to daily step count, the minimum recommended daily amount of 30 minutes of MVPA, accumulated in addition to habitual daily activities (collectively taken in the course of free-living and not necessarily of at least moderate intensity), was estimated to correspond to 7,000-8,000 daily steps in younger adults and to 7,000-10,000 daily steps in older (>65 years of age) adults [21, 30, 33] (Figure 4).

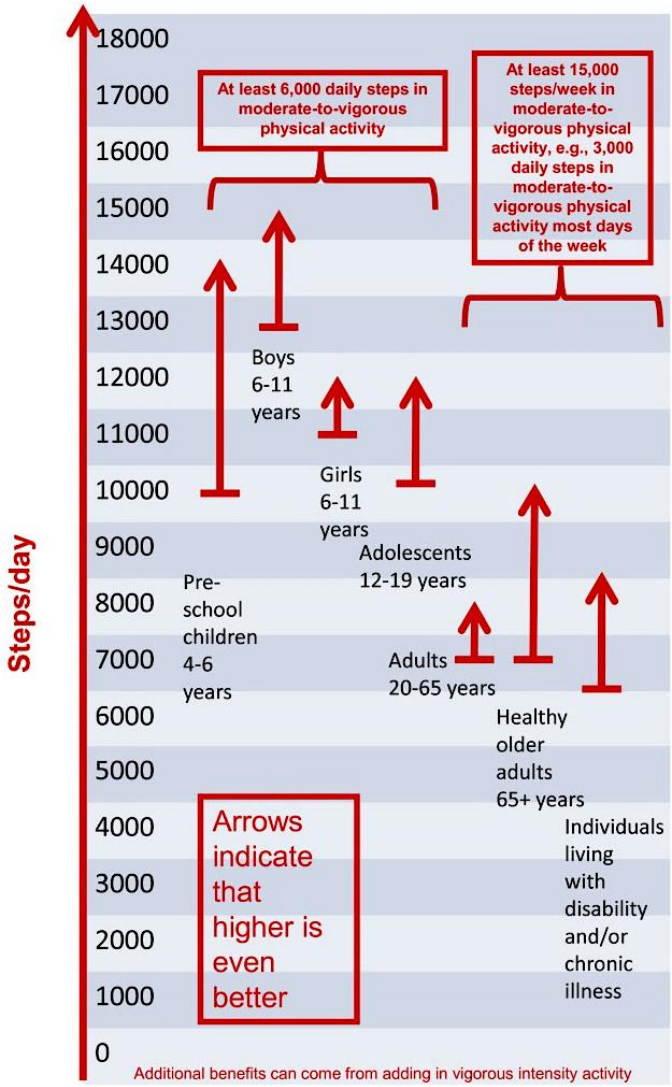


Figure 4: Steps/day scale schematic linked to time spent in moderate-to-vigorous physical activity (From [33]).

Physical activity should not be considered interchangeably with exercise. Exercise is a subcategory of physical activity that is planned, structured, and repetitive with a final or an intermediate objective the improvement or maintenance of one or more components of physical fitness [1]. Physical activity may also not be confused for maximal exercise capacity. The latter can be defined as the maximum amount of physical workload that an individual can sustain through a coordinated cardiovascular, respiratory, and neural response along with the action of exercising muscles. An accurate assessment of exercise capacity requires that maximal physical exertion is sufficiently prolonged to reach a stable (or steady state) effect on the circulation and that the pattern of response is consistent when exertion is repeated, and it is best conducted by cardiopulmonary exercise testing [34]. However, maximal exercise performance assessed by standardized exercise protocols does not correlate sufficiently with PADL in patient populations [35, 36]. Functional exercise capacity as assessed by walking tests also does not always identify with PADL. Self-paced 6-minute walk test, for example, assesses the submaximal level of functional capacity and because most activities of daily living are performed at submaximal levels of exertion, the 6-minute walk distance (6MWD) has been thought to reflect PADL [37]. However, several reports fail to confirm a sufficient correlation between PADL and functional exercise capacity [38, 39].

4. MEASURING PHYSICAL ACTIVITY

Physical activity is a complex behavior and challenging to measure. Several methods exist to measure physical activity including behavioral observations, questionnaires, diaries, motion sensors such as pedometers (measuring number of steps over a given time), accelerometers (measuring both the number of steps and intensity of movement over a given time) and heart rate monitors as well as more laborious and expensive methods such the calorimetry and the doubly labeled water method [40].

The most cost-effective and convenient method of measurement of all types of physical activity in clinical and research practice is the administration of self-report questionnaires. Questionnaires can therefore be used in large-sample/population-based studies. Questionnaires can cover long time frames and are thus also useful in longitudinal studies; however, the bigger the time frame the larger the recall bias it introduces. Due to the complex and subjective information collected, questionnaires may also over- or under-estimate participants' physical activity [41, 42]. Also, older adults are more likely to engage in light- to moderate-intensity physical activity, which is the most difficult type of activity to be assessed by questionnaires [43]. Finally physical activity questionnaires are applicable to the specific clinical and medical conditions for which they have been designed and validated for, including the target population, sample size, age group, recall period, dimension and intensity of physical activity. Therefore, results from studies aimed at evaluating the validity of questionnaires assessed in a certain population cannot be systematically extrapolated to different populations, ethnic groups, geographical regions, or different dimensions of physical activity [44].

In the modern era, accelerometers provide ecologically valid and objective measures of everyday physical activity in a free-living environment. Accelerometers are wearable monitor devices that measure multiaxial (vertical, horizontal and perpendicular) accelerations of the body segment to which they are attached. The signal is usually filtered and pre-processed by the monitor to obtain activity counts (i.e., accelerations due to body movement) per unit of time (most commonly, minutes). The activity counts are then converted by device-specific algorithms into kilocalories and/or METs. Furthermore, the amount of physical activity may be obtained by classifying activity counts accumulated in a specific time interval (epoch length) using a set of cut-points, i.e., intensity thresholds for classification of the intensity of physical activity [45]. Methods to estimate these variables from raw acceleration signals (gravity units) instead of activity counts have also been developed [45].

Accelerometers also have limitations. In order to make the data comparable across types of accelerometers or types of physical activity measurement, each accelerometer model has its own algorithm to convert accelerometer counts into kilocalories and/or METs. This may lead to different output values depending on the model used so that one cannot directly compare data from different models [40]. Depending on the attachment site, single accelerometers are not able to detect all body movements (e.g., upper/lower body or stationary movement) or capture the context in which the measured activities take place (e.g., leisure time or work). Accelerometers require a logistically more complex administration than questionnaires and are battery-dependent. Repeated administration of

accelerometers is therefore required in order to assess seasonal or other kinds of variation in physical activity and their use is impractical in large-sample or long-term studies. Finally, accelerometers may misclassify an individual's physical activity profile because most are not waterproof and must be removed during aquatic activities [40].

5. PHYSICAL ACTIVITY IN DAILY LIFE IN ASTHMA.

Population-based evidence collectively suggests that individuals with asthma are less likely to engage in regular physical activity and less likely to engage in more intense exercise than those without asthma as well as less likely to engage in physical activity at recommended levels [46-50]. A recent systematic review among all available studies using a control group, identified 11 studies (asthma sample = 32,606) reporting less physical activity in asthma, and 6 studies (asthma sample = 7824) reporting no difference thus leading to the conclusion that people with asthma engage in less activity compared to controls [51].

The first ever data on PADL in adults with asthma, derived from objective accelerometer measurements were published only in 2013 [52]. A subsequent, meta-analysis of 7 studies published by 2017 (asthma sample = 526) reporting on accelerometer-counted daily steps revealed a mean of 8,390 daily steps (95% CI 7,361–9,419) among steps patients with mild, moderate or severe asthma [51]. The latter suggests that patients with asthma fall into the “somewhat active” category of a step-defined ladder of physical activity [31, 53]. However, this estimate may be over-optimistic for specific subgroups in the asthma population which are both under-represented and at risk for lower physical activity, such as those with severe asthma (see below) or obesity and the elderly [51]. Importantly, patients with asthma often fail to reach the thresholds of 8,000–10,000 steps per day for people aged <60 years, or 6,000–8,000 steps per day for people aged ≥60 years for reduction in risk of all-cause mortality [5]. In four studies that compared the volume and/or intensity of PADL (including time in MVPA, METs count and energy expenditure) using activity

monitors, people with asthma tend to accumulate less physical activity than healthy controls [51].

Few cross-sectional studies have focused on the objective assessment of physical activity in the important population of patients with severe asthma. Severe asthma is defined as asthma that remains uncontrolled despite adherence with maximal optimized therapy and treatment of contributory factors or that worsens when high dose treatment is decreased [54, 55]. Severe asthma has an estimated prevalence of 5–10% in the total asthma population, and is important because it impacts considerably on morbidity and mortality and accounts for a major share of healthcare utilization and cost as well as socioeconomic cost in asthma [55]. Patients with severe asthma experience a heavy burden of symptoms, increased rate of frightening or unpredictable exacerbations, hospitalizations, and medication side-effects, which interfere with day-to-day living [54, 56]. Severe asthma often affects physical activity, interferes with family, social and working life, limits career choices and vacation options, affects sleep, emotional and mental health [56, 57], leading to poor quality of life (QOL) and impaired lifestyle as compared with patients with well-controlled disease [56].

Studies in severe asthma are consistent in that patients with severe asthma present with considerably low levels of physical activity. Cordova-Rivera and colleagues [58] reported as low as 5362 (median 3999–7817) daily steps and 21.9 (12.8–37.9) minutes of MVPA per day in 61 patients with severe asthma. Compared with controls, individuals with severe asthma accumulated 31.4% (2232) less steps per day and engaged in 47.5% less time per day in MVPA ($p < 0.001$ for both). Time

spent in MVPA has been positively associated with disease control [51, 59] and a 25-minute increase in MVPA was associated with a clinically significant improvement in Asthma Control Questionnaire score of 0.52 units [51]

More recently, Neale et al. [59] reported on significantly lower levels of physical activity in 43 adults with severe asthma compared to 48 healthy controls including daily step count (5,183 ± 2,935 versus 7,755 ± 3,383), time spent doing ≥10 min bouts of MVPA (12 ± 21 versus 36 ± 38) and total time in MVPA (44 ± 46 versus 91 ± 80). After adjusting for body mass index (BMI) and wear-time, adults with severe asthma completed fewer steps and spent less time spent doing sustained (≥10 min bouts) MVPA, but the difference in total MVPA became non-significant. Daily steps were positively associated with disease-specific HRQoL as measured with EuroQol questionnaire, Asthma Quality of Life Questionnaire (AQLQ), and Chronic Respiratory Questionnaire (CRQ), after adjusting for wear-time, age, forced expiratory volume in 1 second (FEV_1) and BMI. Time spent doing ≥10 min bouts of MVPA and total MVPA were also positively associated with AQLQ and CRQ scores [59].

Bahmer et al. [60] reported 6,174 (4,822–9,277) daily steps and 125 (68–172) minutes of at least moderate activity per day in 63 patients with severe asthma, both of which were significantly lower compared to 83 patients with mild-to-moderate asthma (by 21% and 17%, respectively) and 29 healthy controls (by 31% and 23%, respectively), after adjusting for confounders. In a cohort of 23 patients with severe asthma studied by Hennegrave at al. [61], daily steps were 6,560 ± 3,915, daily time in MVPA 120 ± 54 but did not differ significantly from patients with mild-to-moderate asthma. Finally, another cohort of 62 patients with severe asthma presented with

5,385 (3,941–7,844) daily step count and 22.3 (13.3–35) minutes in MVPA [62]. A summary of the available evidence on PADL in patients with severe asthma is provided in Special Part II, Table 6 (page 92).

Data on sedentary time in severe asthma are scarce [51]. In cross-sectional studies examining sedentary time with activity monitors, engagement in sedentary behavior was similar between severe asthmatics and controls but both groups were sedentary [58, 59]; stationary time was not associated with HRQoL [59].

6. CAUSES OF LOW DAILY PHYSICAL ACTIVITY IN ASTHMA.

Compared to healthy controls, young asthmatic patients were found to have similar maximum heart rate but reduced $V\dot{O}_{2max}$, anaerobic threshold and oxygen pulse, suggesting suboptimal fitness [63]. However, reduced fitness in asthmatic patients could not be attributed directly due to airflow obstruction. Lung function (FEV_1) in asthmatics did not correlate with $V\dot{O}_{2max}$, anaerobic threshold, or oxygen pulse either before or after bronchodilator, and asthmaticç had sufficient ventilatory reserve to allow toleration of exercise workload adequate to enhance cardiovascular fitness [63]. Accordingly, nebulized bronchodilator therapy with salbutamol before exercise, albeit convincingly improved FEV_1, had little effect on cardiorespiratory responses such as maximal workload, oxygen uptake, heart rate, and ventilation during progressive maximal exercise in patients with mild asthma [64]. Also, although salbutamol administration increased tidal volume at maximal exercise, it did not change the perception of exertional breathlessness in asthmatic subjects [64]. Finally, the state of airway function —whether bronchodilated or bronchoconstricted— prior to exercise was not found to affect ventilation or operating lung volumes during exercise in mild asthmatics with normal maximal exercise capacity [65]. Therefore, evidence suggests a robust pulmonary system, at least in the mild asthmatics; one that is capable of adequately responding to the demand for acute increase in airflow necessitated by high-intensity aerobic exercise. [65].

Direct evidence on the association between lung function and PADL in asthma remains limited and inconclusive. Weak but significant associations between

physical activity and lung function in general asthma populations have been reported by several cross-sectional studies, as summarized elsewhere [51]. Notably, most of these studies evaluated PADL with questionnaires and activity diaries rather than with objective activity monitors [51]. In a study by van't Hul et al. [66], there were no correlations between accelerometer-derived parameters of PADL and spirometric measures. In another study by Hennegrave et al. [61], although FEV_1 correlated with daily steps (r = 0.41), it was not independently retained in multivariable linear regression analysis for daily steps. Bahmer at al. [60] also did not detect associations between gold-standard airflow limitation measured by FEV_1 and peak expiratory flow rate (PEFR) and daily steps in severe asthmatics. However, daily steps were associated with impulse oscillometric airway resistance and small airway dysfunction [60]. This is important because peripheral airway involvement is highly relevant to the pathophysiology of asthma and it might indicate that impulse oscillometric assessment in a tidal breathing maneuver might enhance our understanding of the consequences of the disease for everyday life, irrespective of the current concept of disease severity in asthma [60].

Physical activity *per se* is a potent stimulus for asthma symptoms and vigorous physical activity is particularly associated with more asthma symptoms [67-69]. Emerging or worsening asthma symptoms during exercise may result in reduced exercise tolerance whereas, fear of experiencing such symptoms may lead many people with asthma to intuitively, or preemptively avoid physical activity. Asthma is associated with adverse, paradoxical responses to physical activity. Up to 90% of asthmatic patients develop exercise-induced bronchoconstriction (EIB), a distinct form of bronchial hyperresponsiveness (BHR) defined as acute, transient narrowing

of the airways during or immediately after cessation of exercise, or strenuous physical activity [70]. EIB in asthma reflects disease control and is thought to result from changes in airway physiology triggered by the large volume of relatively cool and dry inhaled air. Typical symptoms include dyspnea, chest tightness, wheezing, or cough and may result in exercise avoidance. EIB may also occur less frequently in subjects without clinical asthma, particularly in children, athletes, individuals with atopy or rhinitis and after respiratory infections; earlier reports suggest a prevalence of 5% to 20% in the general population. EIB can more commonly be diagnosed by a ≥10 % sustained decrease in FEV_1 after a standardized exercise challenge test; other direct or indirect bronchoprovocative tests may also be used as surrogate diagnostic tools [70].

The status of clinical asthma control is another determinant of physical activity in asthmatic patients. In national representative studies in the United Kingdom [71] and the U.S [72] in patients with moderate-to-severe asthma, those with uncontrolled asthma were at higher risk for limitations in overall physical activity, outdoors activity and daily activity compared with patients with controlled asthma. Elsewhere, parameters of PADL (daily step count, and time in vigorous activity, physical activity level (PAL)) decreased with loss of asthma control [66, 73].

Further research is needed on the effect of asthma severity on PADL. In a small study by Bruno et al. [74], 12 patients with untreated intermittent asthma had lower daily moving time, step count, active energy expenditure (EE) and METs compared to 12 patients with moderate treated asthma. However, Hennegrave et al [61], did not find significant differences between 23 patients with severe asthma and 28

matched patients with mild/moderate asthma in terms of daily steps (6,560 ± 3,915 vs 8,546 ± 3,431), time spent in MVPA (120 ± 54 vs 121 ± 32 min/day), EE in MVPA (620 ± 360 vs 660 ± 140 kcal/day), or total EE (2,606 ± 570 vs 2,666 ± 551 kcal/day); and PADL was not influenced by asthma control *per se*. However, it is possible that the underpowered nature of the study accounts for some of these findings [61].

Demographic factors may account for low activity in asthmatic patients. The impact of obesity and the aging on physical activity should be considered for the large populations of obese [75] and elderly [76] people living with asthma, respectively. Evidence shows that obese patients with asthma present with low-level PADL and they most commonly fail to meet the international recommendations for physical activity [75]. Also, the decrease in activity tends to be more pronounced, or even exclusive, in older people with asthma than their younger counterparts [51]. Plausible biological decline in lung and systemic function, chronicity of asthma and airway inflammation, chronic smoking, accumulating comorbidities as well as older beliefs on physical activity and asthma, may all synergistically render older asthmatics less active. Aging and asthma duration also increase the risk of severe asthma [77]. Finally, physical activity in asthma seems to be influenced by sex with several studies reporting lower physical activity in females with asthma compared to males [51]. This observation follows the trend in physical activity in the general population but may also reflect the fact that female asthmatics are more likely to have severe asthma than males [78, 79].

Frequent comorbidities in asthma including allergic dermatitis, chronic rhinosinusitis, arthritis, gastroesophageal reflux disease, diabetes and

hypercholesterolemia have also been associated with activity limitation in large-scale studies [72]. Also, co-diagnosis of chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes and depression associated with asthma-related hospitalizations and emergency department visits in asthmatics older than 65 years [80]. Psychological distress, anxiety or depression and decreased feelings of control which are common in asthma patients, are significantly associated with physical health status and activity [81, 82] [72]. Psychosocial factors are in fact thought to affect the pathogenesis and pathophysiology of asthma, either directly through autonomic, endocrine, immunological, and central nervous system mechanisms, or indirectly through personal motivations and self-conceptions, lifestyle aspects, health behaviors as well as illness cognition, perception and response including adherence to medication and avoidance of triggers [83]. Accordingly, some atypical causes of exertional dyspnea are more common in asthma, including psychogenic hyperventilation [84] dysfunctional breathing [85] and vocal cord dysfunction [86]. Vocal cord dysfunction is in fact recognized to be present in up to half of patients with severe asthma [82].

Studies show that approximately 20% of asthmatics currently smoke, a prevalence comparable to that found in the general population. Cigarette smoking in asthma patients is associated with several factors that would be expected to result in lower levels of physical inactivity including worse asthma control and severe symptoms, poorer lung function and accelerated lung function decline, worse asthma-related quality of life, increased healthcare use and costs (unscheduled doctor visits and frequent hospital admissions) and higher rate of exacerbations requiring systemic corticosteroids [87, 88].

Eventually, multifactorial restriction of physical activity may lead to the establishment of a vicious circle of physical inactivity, deconditioning, asthma symptoms and obesity among patients with asthma across all ages [89-91]. Obesity has been identified as a risk factor for childhood asthma and wheeze, especially in girls [92] and gain in BMI predisposes to new asthma diagnosis in female young adults [93]. Obesity has also been shown to be more common among asthmatics than non-asthmatics and extremely common in patients with severe asthma, whereas asthma is more common in obese than lean subjects [94, 95]. Obesity and asthma are therefore considered associated diseases and obesity-related asthma is considered a distinct asthma phenotype with more prominent respiratory symptoms, reduced responsiveness to inhaled corticosteroids, worsened asthma severity, more frequent exacerbations and health care use, and generally, more difficult to control [54, 96-99]. This may be due to different type of airway inflammation, low-grade systemic inflammation due to adiposity, contributory comorbidities such as obstructive sleep apnea and gastroesophageal reflux disease, lack of fitness or mechanical factors (e.g. reduction in lung volume due to abdominal fat) contributing to dyspnea [54]. Notably, systemic interleukin (IL)-6 inflammation and clinical features of metabolic dysfunction, which occur most commonly in the subset of obese asthma patients, are associated strongly with more severe asthma [100].

Obesity has been identified as a risk factor for insufficient physical activity in asthma [101]. Conversely, physical activity in asthma has been found to be an independent predictor of fat mass, muscle mass, symptom control and disease

severity [73, 74] whereas, weight loss by exercise reduced medication needs as well as improved lung function, asthma control and asthma-related quality of life [102]. Also, asthmatic patients who were both physically inactive and obese had increased risk for health care use than active and normal weight patients [103]. Thus, it is possible that lower levels of physical activity represent both a cause and consequence of obesity as well as a mediator between obesity and worse asthma outcomes.

7. THE EFFECT OF PHYSICAL ACTIVITY AND EXERCISE ON ASTHMA.

7.1 CLINICAL EFFECT

The possibility of an etiological relation between physical activity and development of incident asthma has been investigated by several studies but the overall quality of evidence remains low due to the cross-sectional design of most of the studies and self-reported diagnosis of asthma and measures of physical activity.

More appropriate for the investigation of causal relationships are longitudinal studies in which the exposure (physical activity) precedes the outcome (onset of asthma). A 2022 systematic meta-analysis of 4 longitudinal studies with a considerable total accrued number of subjects (n = 84,319) and duration (5 to 10 years) concluded that patients with high-level physical activity had a lower risk of developing asthma compared with patient with low-level physical activity (odds ratio (OR) = 0.87, 95% credible interval (CrI): 0.78 to 0.95 [104]. A previous systematic review of 5 longitudinal studies (n = 85,117, duration 5 to 11 years) also indicated that physical activity is a possible protective factor against development of asthma (OR for incident asthma 0.88, 95% CI 0.77 to 1.01) [105]. However, it must be noted that these results were not adjusted for potential confounding factors such as age, sex, body mass index, smoking status, education, socioeconomic status, and comorbidities that could be associated with both low habitual physical activity and development of asthma [104, 105].

Large national (n = 18,894 Norwegians adults; duration 11 years) [106] and multinational longitudinal studies (n = 3,503 adults from 25 countries in Europe and Australia; duration 10 years) [107] that checked for potential confounding factors did not find evidence that overall physical activity [106] or vigorous physical activity during leisure [107] reduced the risk of asthma developing in adults. A pediatric longitudinal study in the Netherlands that checked for confounding factors, also did not find an association between accelerometer-measured physical activity and development of wheezing or shortness of breath in 347 pre-school children [108].

Nonetheless, robust evidence links physical activity to significant clinical outcomes in asthma. A study of 2,818 U.S. women with asthma has shown higher levels of regular physical activity to reduce the risk of asthma exacerbations and hospital admission, independent of asthma severity and other covariates [109]. Conversely, physical inactivity in U.S. and Canadian populations was associated with more frequent asthma symptoms, medication use, medical consultations, emergency hospital visits, overnight hospital stay and poor sleep quality [88, 103, 110]. Multiple logistic regression models in a U.S. population-based study (n = 12,111 with current asthma), identified physical activity as a significant determinant of measures of quality of life in asthma such as poor or fair health, number of physically unhealthy days, number of mentally unhealthy days, and number of activity limitation days [111].

These robust findings support the recommendation of regular physical activity in individuals with asthma. In addition to their known cardiometabolic and other health benefits, increasing PADL via low-cost, accessible means (e.g., walking) or

pursuing more frequent and longer breaks of sedentary behavior may be disease-specific beneficial interventions for many individuals with asthma [51, 89].

8.1 PHYSIOLOGICAL EFFECT

Physical activity and exercise may have protective properties against asthma via mechanical stimulation of airway epithelial cells [112]. The latter causes apical release of ATP and elevation of intracellular calcium, which increases ciliary beat frequency and speeds up mucociliary clearance [113]. Also, deep inspiration and increased sigh rate during physical activity are thought to stretch the airway smooth muscles and help maintain a normal tone and bronchiole patency [112].

Longitudinal studies provide evidence for a beneficial effect of physical activity on lung function of patients with asthma. In a population-based cohort of 1329 adults with asthma in Norway [114], there was evidence of slightly less lung function decline in physically active participants compared with the inactive ones. On average, active asthmatics had 1.5–2.1% less decline in the FEV_1/FVC ratio and 44–88 mL less decline in PEFR during the 11.6-year follow-up [114]. In another cohort of 201 individuals in Finland who were followed for 12 years after diagnosis of asthma, those with high physical activity had slower annual FEV_1 decline (−41.4 ml vs. −58.8 ml, $p < 0.001$) and FVC decline (−29.3 ml vs. −43.6 ml, $p < 0.018$), compared with those with low physical activity [115]. Also, the high physical activity group had higher FEV_1 values at follow-up, and higher FEV_1/FVC ratios at diagnosis and follow-up [115].

8.1 BIOLOGICAL EFFECT

Physical activity and exercise impact on immune and metabolomic pathways in asthma. Airway inflammation is a principal feature of asthma that is associated with increased disease severity and increased risk of exacerbation, whereas exercise has systemic and airway anti-inflammatory effects [58, 116-118]. Animal and human studies in asthma have identified several exercise-induced anti-inflammatory molecular effects including reduction in serum T helper 2 proinflammatory cytokines (IL-4–6 and IL-13–16), monocyte chemoattractant protein 1 and keratinocyte chemoattractant protein (murine homologue to human IL-8), inhibition of nuclear factor kappa B activation, as well as increases in circulating regulatory T cells and anti-inflammatory factors including IL-10, interferon-gamma and IL-1 receptor antagonist [119-127].

At a tissue and organ level, aerobic exercise decreases eosinophilic airway inflammation, bronchial remodelling and respiratory mechanics in animal models of asthma as suggested by reduction in eosinophil count in bronchoalveolar lavage fluid, airway walls and sputum, as well as reduction in peribronchial inflammatory cell count, mucus synthesis, smooth muscle thickness, airway resistance and elastance [122-124, 128, 129]. Although not a constant finding among asthmatic patients, exercise may also reduce the airway inflammation as measured by exhaled nitric oxide (FeNO) as well as the nasal inflammation as measured by eosinophilic cell count resulting in sustainable improvements in allergic symptoms [119, 129-131].

Physical activity and exercise are also beneficial for reducing C-reactive protein (CRP) in asthmatic individuals [132]. CRP is a systemic inflammatory marker; in absence of any other systemic inflammatory disease, reduction in CRP could presumably be due only to a reduction in airway inflammation [132]. In patients with severe asthma, increased PADL was associated with lower systemic inflammation (for every increase of 1,000 steps per day, high sensitivity-CRP was reduced by 13%) after adjustment for confounders, albeit no associations were found with measures of eosinophilic airway inflammation [58].

Metabolomics is the study of the metabolite composition (ie, the metabolome) of a cell type, tissue, organ, or organism. The metabolome is the collection of endogenous small molecules that mark specific fingerprints of cellular biochemistry. Metabolomics measures global sets of low-molecular-weight metabolites (including amino acids, organic acids, sugars, fatty acids, lipids, steroids, small peptides, and vitamins), providing a snapshot of relevant biological processes. It provides a readout of metabolic activity status in relation to genetic variations, gene expression, or external stimuli. Such external stimuli include infections and allergens, in which a specific metabolomic profile marks interaction between the environmental agent and the host molecules (i.e., gene-environment interactions; DNA, RNA, proteins, lipids, and other enzymes). Metabolites, in addition to being produced directly by the host organism, can be derived by host microbiota, as well as transformed from xenobiotic, dietary, and other exogenous sources [133]. Several individual metabolites and metabolomic profiles measured in exhaled breath condensate, urine, plasma, and serum could identify people with asthma and asthma phenotypes with high discriminatory ability [134].

Most of the literature to date concludes that varying degrees of physical activity or exercise induce, or are associated with, quantifiable alterations in the metabolome mainly in fatty acid metabolism, mobilization and lipolysis, the tricarboxylic acid cycle, glycolysis, amino acid metabolism, carnitine metabolism, purine metabolism, cholesterol metabolism and insulin sensitivity among others [135]. The evidence points to a multifactorial dose response relationship between physical activity/exercise and its effect on the metabolome, incorporating intensity, bout length, frequency and time frame of exposure (hours, days, weeks, years) [135]. The microbiome profile of cardiorespiratory fit individuals specifically appears to favor gut production of butyrate, a short-chain fatty acid (SCFA) and a common indicator of gut health, independent of diet [136]. SCFAs have been shown to promote dendritic cell hematopoiesis, impair the promotion of Th2 effector cells, thus inhibiting allergic inflammation in animals; they also decrease allergic effector T cell responses, promote formation of T regulatory cells and reduce nuclear factor kappa B activation in macrophages [89]. These findings link physical activity to SCFAs and altered innate and adaptive immune responses and may suggest a metabolomic link between physical activity and asthma [89]. Physical activity has also been shown to reverse the effects of a high fat diet on gut microbiome in animal models [137-139].

8. INTERVENTIONS TARGETING PHYSICAL ACTIVITY IN ASTHMA

8.1 EXERCISE TRAINING AND PULMONARY REHABILITATION

To date, more than 20 randomized controlled trials (RCT) have collectively reported benefits of supervised aerobic exercise training on a range of outcomes in adult patients with asthma such as exercise capacity, airway inflammation, disease exacerbation, clinical control, health-care use, psychosocial symptoms and asthma-related quality of life [119, 140-148]. In the largest and most recent RTC including 89 subjects with mild or moderate asthma, aerobic exercise at least three times a week for ≥ 30 minutes plus muscle training, and stretching, improved asthma control and reduced shortness of breath [141]. The effect of intervention on improving asthma control was 23% (risk reduction = 0.23, 95% CI 0.027–0.438) and 30.1% for shortness of breath (risk reduction = 0.301, 95% CI 0.109–0.49). Qualitative findings of systematic review of the RCTs also suggest that exercise training can improve asthma control, lung function, and health care related quality of life [149, 150], with only a small minority of studies reporting no improvements in any of these outcomes. None of the studies found worsening of asthma control during the physical activity interventions.

A systematic review and meta-analysis of 18 RCTs in adult patients (n = 1,073) found that exercise training was effective in improving HRQoL and asthma control (standard mean difference =−0.80, 95% CrI −1.30 to −0.31), FEV_1%predicted (weighted mean difference (MD) = 0.47 , 95% CrI 0.03 to 0.90), and $\dot{V}O_{2max}$ (weighted MD = 1.18 $mL.kg^{-1}.min^{-1}$, 95% CrI: 0.87 to 1.48) [104]. A meta-analysis of 17 RCTs including 599 children and adult asthmatics, also reported that exercise training led

to a significant improvement in days without asthma symptoms (MD 8.90 symptom-free days, 95 % CI 8.18–9.61) [151]. These findings are promising although they stem from relatively small individual cohorts attending structured training sessions at well-resourced, designated centers or led by physiotherapists, which are not generalizable to many real-world settings [89]. The heterogeneity in the type, frequency, and duration of exercise protocols among the studies (including various types of land-based exercise methods such as walking, running, jogging, cycling, strength training, or a combination of these at both low and high-altitude settings, for variable duration between 3 to 24 weeks) reflects the knowledge gap on the optimal exercise regime and the absence of relevant guidelines and preclude a collective review of the evidence [151].

From a physiological scope, exercise training may enable weight loss [127] and evidently improve cardiopulmonary fitness [9], whereas its impact on lung function is less clear. A 2013 Cochrane metanalysis of RTCs of people over eight years of age with asthma showed significant improvement in $\dot{V}O_{2max}$ with land-based exercise training (MD 4.92 $mL.kg^{-1}.min^{-1}$; 95% CI 3.98–5.87; 8 studies, 267 participants) without significant effects in other measures of pulmonary function such as FEV_1, FVC, minute ventilation at maximal exercise or PEFR [9]. The improvement in cardiopulmonary fitness is important because it may independently reduce the risk of dyspnea due to deconditioning and other conditions unrelated to airflow limitation that may mistakenly attributed to asthma [9]. This would essentially enable a better effort-benefit ratio, leaving more breathing reserves for activities of daily life [141]. Also, collective evidence suggests that physical training may have positive effects on asthma symptoms and health-related quality of life,

with the majority of studies producing a statistically and clinically significant benefit [9, 152]. A meta-analysis in children and adult asthmatics also showed that exercise training led to a significant improvement in exercise capacity (MD 4.06 $mL.kg^{-1}.min^{-1}$, 95 % CI 3.02–5.10 for $\dot{V}O_{2max}$; MD 24.03 W, 95 % CI 20.15–27.9 for W_{max}; standardized MD 0.81, 95 % CI 0.13–1.48, for exercise endurance) [151] but a questionable change in FEV_1 (MD 0.09 L, 95 % CI 0.00–0.17, p = 0.05) compared with usual care. However, the analysis of relative within-group changes after exercise training (in both RCTs and controlled trials) showed small improvements in FEV_1 (3 ± 7 %, p = 0.019) compared with control conditions and multiple linear regression modelling revealed that changes in lung function, along with changes in BHR, contributed significantly to the observed improvement in the quality of life [151]. Nonetheless, the magnitude of the effect of exercise training on lung function may have been hampered by the limited time frame of these interventions.

Exercise training has been shown to have a beneficial effect in reduction of BHR. In a RCT by Franca-Pinto, aerobic training led to a reduction in BHR by 1 doubling dose (95% CI 0.3 to 1.7 doubling dose) in patients with moderate or severe asthma following exercise training [119]. In that study, patients with higher airway inflammation (baseline FeNO ≥ 26 ppb and ≥ 3% sputum eosinophils) and worse asthma control also experienced reduction in sputum eosinophils and FeNO [119]. In an analysis of relative changes in available non-controlled, controlled and randomized controlled trials in children, adolescent and adult patients with asthma, exercise training in the form of land-based exercise or swimming was shown to improve BHR by 53% and EIB by 9% compared with control conditions; also, improvements in BHR explained part of the observed improvement in quality of life

and exercise capacity [151]. Animal studies suggest that aerobic exercise training attenuates BHR via a mechanism that involves β2-adrenergic receptors [153].

Swimming is often recommended as a form of exercise for asthmatics due to the humidified and warm air, low pollen count exposure and hydrostatic pressure on the thoracic wall [154], although some concerns exist about chlorine exposure with indoor pools [54]. In a systematic review of 8 studies (n = 262) of children and adolescents with asthma, swimming programs have been shown to increase cardiopulmonary fitness (mean $\dot{V}O_{2max}$ increase 9.67 $mL.kg^{-1}.min^{-1}$, 95% CI 5.84–13.51 (2 studies; n = 32) and improve lung function (FEV_1; 0.1 L higher, 95% CI 0–0.2 (4 studies; n = 113) in a clinically meaningful fashion compared to usual care. [154]. However, there was no statistically significant difference between swimming and usual care/other physical activities on quality of life, asthma control, exacerbations and medication use to recommend swimming over other forms of physical activity [154]. Water-based exercises in adults have been less researched. A Cochrane systematic review of 3 available studies including 136 adult participants who followed swimming and water aerobics was unable to assess the place of water-based exercise in asthma due to the small number of participants, the clinical and methodological heterogeneity observed, and the high risk of bias assessed [155]. Nonetheless, engagement of patients with mild persistent asthma in recreational swimming in non-chlorinated pools, combined with regular medical treatment and education, led to better improvement in lung function and more significant decrease in BHR (2.01 vs. 1.75; $p < 0.001$) compared with standard care [156].

The effect of exercise training at high altitude has also been investigated in asthmatic populations. High-altitude treatment has long been recommended and applied as beneficial in asthma due to lower allergen exposure, less air pollution and lower air humidity [157, 158]. Decreased air density at altitude also reduces airway resistance, which might increase exercise capacity [157]. A RCT found that high- and low-altitude-rehabilitation programs with endurance exercise training for 3 weeks were similarly highly effective in improving asthma control in patients with poorly controlled asthma —a benefit which was preserved after 3 months [145]. High-altitude training led to better improvement in PEFR-variability, exercise capacity and airway inflammation as assessed by FeNO compared to low-altitude training [145].

Athletes with asthma represent a distinct asthmatic population from which lessons can be gleaned. EIB (often without respiratory symptoms) and asthma occur frequently and increasingly in athletes, reaching an estimated prevalence between 30% and 70% among elite athletes, depending on the type of sport performed [159, 160]. Athletes may have already had BHR and asthma before taking up sports, or may have developed them since becoming active in sports. Phenotypic distinction of asthma in athletes to “atopic asthma” defined by allergic sensitization, rhinitis, allergic comorbidities and increased FeNO; and “sports asthma”, defined by exercise-induced respiratory symptoms and BHR unrelated to allergy but related to specific type of sport and environment, has been proposed [161]. The development of BHR, EIB and asthma in athletes is thought to be due to the high frequency of repeated physical strain and excessive ventilation occurring during training and competitions as well as the ensuing overexposure to environmental factors, allergens and irritants such as cold and dry air, air pollution and organic chlorine

compounds. Accordingly, BHR, EIB and asthma are more common in endurance sports, particularly winter sports and swimming [159, 162, 163]. Nonetheless, as the various achievement of asthmatic athletes in competitive sports can attest, asthma can usually be well managed in athletes, most often with the use of maintenance inhaled glucocorticoids and inhaled short-acting β_2-agonists along with warm-up before exercise and, therefore, allow for maximal performance. Of note, currently used inhaled β_2-agonists have no performance-enhancing effect in athletes with or without asthma and are therefore permitted to use by World Anti-Doping Agency (WADA; for salbutamol the maximum daily dose permitted being 1600 μg). However, their regular or frequent uses may lead to tolerance and decrease in their bronchoprotective effect during exercise [159].

A RCT by Toennesen et al. [147] showed that 2-month high-intensity interval training (spinning) combined with high protein/low glycemic index diet improved asthma control and asthma-related quality of life in nonobese adults with asthma, although these effects were proven non-sustainable at 1-year follow-up [164]. This is of interest because dietary habits have been associated with levels of systemic inflammation, which is relevant to asthma. Epidemiological evidence suggests that a high-fruit and vegetable diet (high in antioxidants) is associated with lower risk of asthma and lung function decline [54]. In contrast, a low-fruit/low-vegetable diet (low in antioxidants) has been associated with increased circulating CRP and increased risk of asthma exacerbations [165]. Consumption of pro-inflammatory foods (e.g., saturated and trans fatty acids) was associated with reductions in low-grade systemic inflammation (plasma IL-6 concentrations) and FEV_1 [166]. This line of evidence sets the scientific rationale for further research on multicomponent

interventions targeting physical activity, diet and weight management in patients with asthma.

Few small RCTs have studied the effect of structured exercise training on PADL. In a trial by Coelho et al. [167], 20 patients with moderate-to-severe asthma showed a significant increase in daily steps and 6MWD compared to controls (average adjusted difference of 2488 steps and 21.9 m, respectively) at 12 weeks of an unsupervised pedometer-based exercise programme. However, the differences became not significant 24-28 weeks after randomization [167]. Turk et al. [148] showed that a 3-month pulmonary rehabilitation program incorporating supervised high-intensity interval training, when combined with an internet-based self-management program increased daily steps by 3097 from baseline in 9 obese patients with BMI ≥ 30 $kg \cdot m^{-2}$ and poorly controlled asthma. In the same study, 14 patients who attended pulmonary rehabilitation alone (without the internet-based self-management program) showed no difference in daily steps and PAL compared to control patients who received usual care but they showed 3200 more daily steps than the controls after 12 months of follow up [148]. Evaristo et al. [168] also found no significant difference in daily steps in 29 patients with moderate-to-severe asthma who completed a 12-week supervised aerobic exercise program and 25 patients who were randomised for breathing exercises. However, both groups increased daily step count by approximately 2,000 steps after the interventions. Finally, in a trial by Freitas et al. [98], an exercise training program combined with a weight loss program improved PADL in 55 grade II obese adults with asthma compared to weight loss alone. In this study, exercise training included supervised aerobic and resistance exercises twice weekly for 3 months plus recommendations

for increasing PADL; the weight loss program included 12 individual hypocaloric diet counseling sessions and was supported by behavioral techniques based on the transtheoretical model. After 3 months, patients who attended both exercise training and a weight loss program group presented a significant increase in daily step counts (3,068 ± 2,325 vs 729 ± 1,118 steps), time spent in MVPA (18.2 ± 17.9 vs 7.9 ± 13.8 min/day), time spent in light-intensity physical activity as well as the number of asthma symptom-free days (14.5 ± 9.6 vs 8.6 ± 11.4 days/months) compared with patients who attended only the weight loss program [98].

A random-effects meta-analysis of 3 of the above studies [98, 167, 168], showed an overall significant mean difference of 1588 (95% CI 399 to 2778; n = 142) daily steps post-intervention between groups in favor of physical activity interventions [150]. The magnitude of effect, however, differed by intervention type, ranging from small to large (Figure 5) [150].

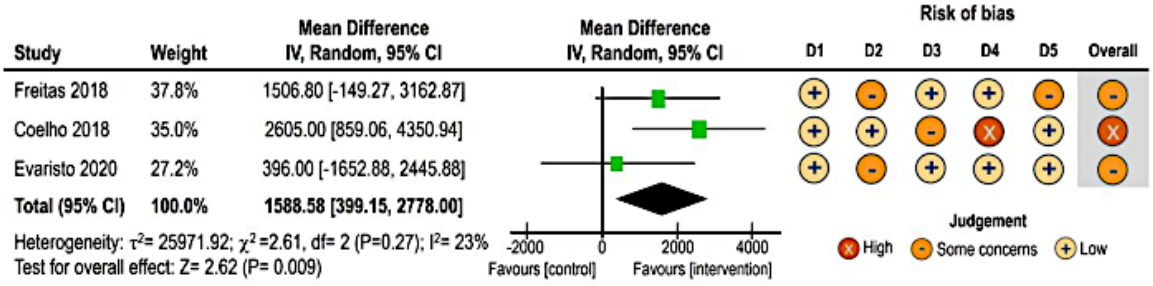


Figure 5: Meta-analysis of randomized controlled trials examining the effect of physical activity interventions versus control on steps per day (post-intervention). D1: Bias arising from the randomisation process; D2: Bias due to deviations from the intended intervention; D3: Bias due to missing outcome data; D4: Bias in measurement of the outcome; D5: Bias in the selection of the reported result (From [150]).

Based on the available evidence and clinical experience, current guidelines recommend exercise as supplementary to medication therapy and support the inclusion of individuals with asthma in pulmonary rehabilitation programs [169, 170]. However, evidence to date remains insufficient to recommend one form of exercise training over another [54]. Preexercise bronchodilators and gradual warm-up are indicated to prevent or minimize EIB [54, 169].

Nonetheless, the long-term effect of exercise interventions on PADL in asthma deserves more research and understanding. This important knowledge gap cannot be bridged by extrapolations from the acute effect of training on exercise capacity and other asthma-specific outcomes. PADL reflects complex behavioral patterns that may not be easily reformed by short-term or singular interventions and paradigm from patients with COPD suggests that changing physical activity behavior needs a long-lasting interdisciplinary approach, bringing together respiratory medicine, rehabilitation sciences, social sciences, and behavioral sciences and best taken within the frame of pulmonary rehabilitation [171].

8.2 PHARMACOLOGICAL INTERVENTIONS

At this time, evidence on the potential effect of available therapies on physical activity in asthma is scarce.

Biologic therapies in the form of monoclonal antibodies target specific pathways and molecules which are important in the pathogenesis of asthma and are increasingly used in patients with severe asthma. In a pilot study of patients with severe asthma, Carpagnano et al. [172] investigated and compared the effect of biologic therapy (30 patients who received either omalizumab or mepolizumab) versus traditional treatment (20 patients) on accelerometer-assessed PADL. At 6 months of therapy, all subjects improved their daily step count and energy expenditure levels but the gain with biologic therapy as a whole was significantly greater than with traditional therapy at 1, 3, and 6 months of follow up. Notably, patients in the biologic therapy arm almost doubled their daily step count (from 3,806 ± 421 to 6,545 ± 844 steps) at 6 months [172]. There was no difference in outcomes between patients on omalizumab and mepolizumab. These are promising findings that leave scope for further research in the relationship between biologic therapies and PADL in asthma.

8.3 BEHAVIORAL INTERVENTIONS

Increasing engagement in PADL requires lifestyle and behavior modifications through targeted interventions [173]. Behavior change interventions aim to increase participant's confidence and self-efficacy to demonstrate the desired behavior through education, motivation, action planning and support. Individual behavior change techniques include goal setting, behavior contract, monitoring, feedback, avoidance strategies, and problem solving/coping planning [174]. In asthma, the appropriate choice of the inhaler device based on patient characteristics, inhaler-technique training and counseling on the importance of adherence to therapy are also key elements for successful outcomes [175].

In a randomized trial of 252 adults with stable, mild-to-moderate asthma, a multicomponent protocol of asthma education, self-monitoring with pedometer, behavior contract plus additional positive affect and self-affirmation components, resulted in clinically important increases in PADL [176]. Energy expenditure increased to 4 months and was sustained through closeout at 12 months. These gains were achieved without exacerbating asthma, and in most cases asthma improved [176]. In another RCT of 51 adults with moderate-to-severe asthma, a comprehensive behavior change intervention on top of usual care and disease-specific education, increased daily step count by 3,605 (1,937 to 8,867) steps and produced improvements in asthma clinical control, sedentary time, sleep quality, and anxiety symptoms [177]. The behavioral intervention included counseling on physical activity combined with a monitoring-and-feedback tool aiming to increase physical activity levels and it was delivered over 8 weekly, face-to-face goal-setting consultations, each lasting 40 minutes [177].

A conceptual model for the interrelationship between asthma, physical activity and targeted interventions is presented in Figure 6.

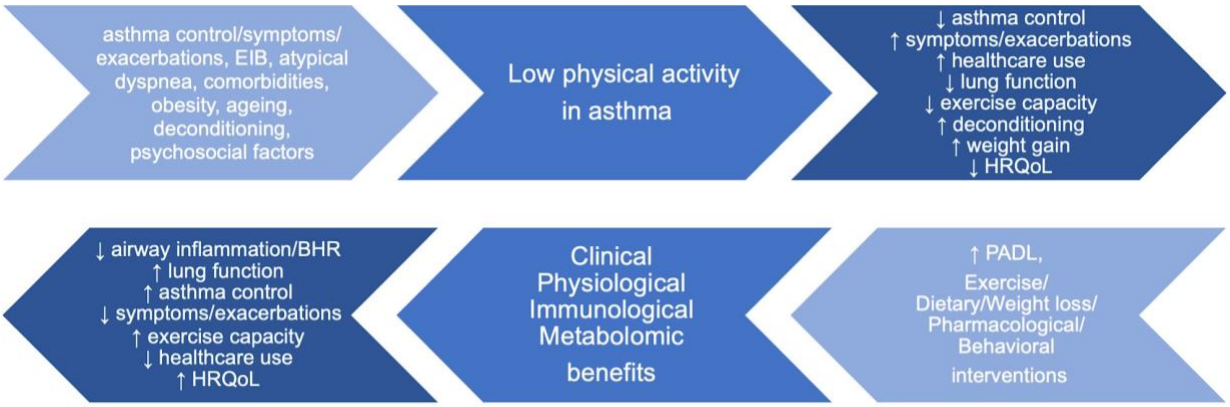


Figure 6: Conceptual model for the interrelationship between asthma, physical activity and targeted interventions. EIB: exercise-induced bronchoconstriction; HRQoL: health-related quality of life; BHR: bronchial hyperresponsiveness (Adapted from [178]).

9. CONCLUSIONS

The relationship between asthma and physical activity is bidirectional and multifaceted. The ultimate goals of contemporary asthma management are required to include the minimization of symptoms so that individuals with asthma can lead normal lives, including engagement in recommended levels of PADL, exercise training or competitive sports. Likewise, higher adherence to physical activity, beyond its general health benefits, is emerging as a key factor for favorable outcomes in asthma including improved lung function, disease control, exacerbation rate, and healthcare use. Our better understanding of the nature of asthma, the advent of effective pharmacological therapies, and relevant research have led to a paradigm shift in the management asthma with regards to physical activity over the course of the last decades but evidence shows that PADL in asthma remains low, especially in the severe form, and PADL represents a challenging area for interventions in that it reflects well-established behavioral patterns. In the modern era of patient-centered healthcare, further reversal of this adverse situation to a virtuous cycle of enhanced physical activity and improved asthma outcomes represents a meaningful and achievable goal. To this goal, further research is needed on the interrelationship between physical activity, airway inflammation and hyperresponsiveness, lung function and clinical outcomes as well as for the identification and clinical implementation of beneficial interventions for PADL in asthmatic patients.

II. SPECIAL PART

(ORIGINAL RESEARCH)

ABSTRACT

Background: For the various asthma-specific beneficial effects of physical activity, physical activity in daily life (PADL) and the potential of asthma therapies on PADL require better characterisation. Hence, we aimed to determine a) PADL of asthma patients, and b) the effect of add-on mepolizumab on PADL of severe asthma patients.

Methods: Adult outpatients with mild-to-moderate or severe asthma had accelerometer assessment of PADL. Severe asthma patients who were commenced on mepolizumab had their PADL reassessed after 12 months.

Results: For the total cohort (n = 36), daily step count, time in moderate-to-vigorous physical activity (MVAP), MVPA volume and Movement Intensity (MI) were 7,806 ± 3,823 steps, 123 (interquartile range, 63) min, 657 ± 255 MET·min and 1.96 (0.45) m/s^2, respectively. All patients met at least one recommendation for PADL but less than half met recommendations for vigorous PADL. Patients on mepolizumab therapy increased daily step count (646 steps; 9%), time in MVPA (20 min; 21%), MVPA volume (87 MET·min; 17%) and MI (0.11 m/s^2; 6%) for the same amount of moving time; lung function, asthma control and health-related quality of life also improved.

Conclusion: Analysis of the first national data on PADL in asthma and novel comparison against current applicable guidelines and other identified beneficial thresholds, showed borderline levels of PADL with room for improvement especially

for severe asthma patients. In a non-sedentary cohort of severe asthma patients, mepolizumab conferred significant and meaningful improvements in PADL.

ClinicalTrials.gov Identifier: NCT03739320

Keywords: asthma; severe asthma; daily physical activity; step count; moderate-to-vigorous physical activity (MVPA); vigorous physical activity; movement intensity; guidelines; accelerometer; mepolizumab.

1. INTRODUCTION

Asthma is a heterogeneous chronic inflammatory disease of the airways that 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 limitation [54]. With a prevalence of 1-18% in different countries, asthma is affecting millions of people across all ages and continues to carry substantial morbidity, mortality and socioeconomic burden globally [54, 179, 180].

Following the modern paradigm of other chronic conditions, physical activity is becoming of increasing interest in asthma. Increasing insight in the nature of asthma and effective management have allowed for a paradigm shift towards active lifestyle. Enhancing and achieving normal levels of physical activity in daily life (PADL) is increasingly considered an important element for successful management and outcomes in asthma. Beyond benefiting all-cause mortality, risk of cancer and chronic disease, health-related quality of life (HRQoL) and other important aspects of general health, physical activity exerts asthma-specific effects. Consistent evidence links higher levels of physical activity with favorable pathophysiological and clinical effects in asthma including improved airway inflammation and hyperresponsiveness, lung function, asthma control, exacerbation rate, and healthcare use [178]. However, evidence also shows that patients with asthma, especially the type of severe asthma, often engage in sedentary levels of physical activity and at lower levels than controls [51, 58]. This line of evidence sets the scientific rationale for further study of the levels and patterns of physical activity in asthma but also, effective interventions to promote the physical activity of patients with asthma.

Biologic therapies are rapidly transforming the management and outcomes of patients with severe asthma. Although severe asthma has a low estimated prevalence of 3–10% in the total asthma population, it represents the most challenging and important type of asthma by disproportionately affecting high on morbidity and mortality and accounting for a major share of healthcare utilization and cost as well as socioeconomic cost in asthma [54, 55]. In the eosinophilic phenotype of severe asthma, mepolizumab, an anti-interleukin(IL)-5 biological therapy, reduces asthma exacerbation rates and corticosteroid use and improves asthma control and HRQoL [181-183]. However, the potential effect of mepolizumab —or other biological therapies— on PADL in patients with severe asthma is insufficiently explored.

Therefore, this study aims to determine both a) the levels of PADL in patients with mild-to-moderate and severe asthma and cross-reference them with current guideline recommendations and b) whether mepolizumab add-on therapy improves PADL in patients with severe eosinophilic asthma.

2. MATERIALS AND METHODS

2.1 PATIENTS

The study was conducted in a prospective, observational design. It consisted of 2 arms of parallel design: 1) the physical activity arm, and 2) the mepolizumab arm. For the physical activity arm, consecutive patients above 18 years old with adequately established and documented asthma of any severity who attended the Asthma Outpatient Clinic, “Sotiria” Chest Diseases Hospital were eligible. Eligible patients for the mepolizumab arm, were those who additionally met the definition of severe asthma [55] and predetermined criteria for mepolizumab therapy [184]. The decision-making for add-on mepolizumab therapy in eligible patients was based exclusively on clinical criteria. Patients were administered 100 mg of mepolizumab (Nucala; GlaxoSmithKline, London, UK) once every 4 weeks for 12 months by subcutaneous injection into the upper arm. Included asthma patients were allowed to be smokers, to avoid significant selection bias [60]. Patients identified as smokers (i.e., either current smokers or former smokers with $\geqslant$10 pack-years) were accurately screened for features distinguishing asthma from COPD, and excluded from the study if features of COPD currently prevailed [185]. Exclusion criteria for both study arms included current or recent (within 4 weeks prior to the study entry) severe exacerbation [55] and comorbidities interfering with physical activity such as musculoskeletal and neurological conditions.

Severe asthma, according to European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines is defined as asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic

corticosteroids (GINA 4–5 level of medications) to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy [55]. Any one of the following four criteria qualifies a patient as having uncontrolled asthma: a) poor symptom control (i.e., Asthma Control Questionnaire (ACQ) score consistently ≥1.5 or Asthma Control Test (ACT) score <20); b) frequent severe exacerbations, defined as two or more exacerbations requiring bursts of systemic corticosteroids (≥3 days each) in the previous year; c) serious exacerbations, defined as at least one hospitalization, intensive care unit stay or mechanical ventilation in the previous year; 4) airflow limitation, i.e., forced expiratory volume in 1 s (FEV_1) <80% predicted (in the presence of reduced FEV_1/forced vital capacity (FVC) defined as less than the lower limit of normal) following a withhold of both short- and long-acting bronchodilators [54]. Patients who do not meet the criteria for uncontrolled asthma, but whose asthma worsens on tapering of corticosteroids (or additional biologics), will also meet the definition of severe asthma. These definitions require patients to be evaluated and managed by an asthma specialist for more than 3 months and relevant modifiable factors such as inhaler technique, adherence, smoking and comorbidities have been addressed.

We followed the recommended criteria for mepolizumab therapy including blood eosinophil count ≥300/μL within the 12 months prior to screening or ≥150/μL at screening (within 6 weeks of dosing) [184].

2.2 CLINICAL ASSESSMENT

At the study entry point, the most recent values of FEV_1, FVC and eosinophil blood count were retrieved from the medical record. All subjects also completed the ACT questionnaire and the “past 4 weeks” version of St. George's Respiratory Questionnaire (SGRQ). Patients on mepolizumab arm also completed the Global Rating of Activity Limitation questionnaire (GRALQ) before and after therapy, and the Global Impression of Change in Activity Limitation questionnaire (GICALQ) after therapy.

The ACT questionnaire consists of 5 items, with 4-week recall and assesses the frequency of shortness of breath and general asthma symptoms, use of rescue medications, the effect of asthma on daily functioning, and overall self-assessment of asthma control [186]. Scores range from 5 (poor asthma control) to 25 (complete control of asthma), higher scores reflect greater asthma control. ACT score > 19 indicates well-controlled asthma. The minimally important difference of the ACT has been found to be 3 points between two groups or for changes over time [187].

The SGRQ is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease [188]. It consists of a 50-item questionnaire with 76 weighted responses split in 2 parts (3 components) and it takes 8-15 minutes to complete. Part 1 assesses symptoms (frequency & severity) with a 1, 3 or 12-month recall (best performance with 3- and 12-month recall); Part 2: Activities that cause or are limited by breathlessness; Impact components (social functioning, psychological disturbances resulting from airways disease) refer to current state as the recall. The

scoring ranges from 0 to 100 for each component, where a higher number is indicative of poorer health. A total score is also calculated from all items, providing a global estimation of the patient's respiratory health [188]. The SGRQ has good discriminative and evaluative properties and is responsive to therapeutic trials. It was developed and validated in both asthma and COPD, although it has also been validated for use in bronchiectasis and has been applied to patients with sarcoidosis. There is a large literature concerning the use of the questionnaire in many settings, including normal values. Based on empirical data and interviews with patients, a mean score change of 4 units in SGRQ is considered for slightly efficacious treatment, 8 units for moderately efficacious treatment and 12 units for very efficacious treatment [189]. For the calculation of the final score we used a commercially free application [190] available at http://sgrq.github.io/. For the purposes of the current study, we used the official Greek translation of the "past 4 weeks" version of SGRQ, which was provided to us free of charge, upon request by the St. George's University of London Medical School.

For the GRALQ, patients were asked to rate their impression of activity limitation in a 4-point scale (please rate your activity limitation). For the GICALQ, patients were asked to rate their activity limitation in a 7-point Likert scale, ranging through much, better, better, slightly better, no change, slightly, worse, worse, and much worse; thus, providing a brief, stand-alone assessment of their perception for their global functioning prior to and after initiating therapy. Both GRALQ and GICALQ have been used in a randomized, double-blind, placebo-controlled efficacy study for mepolizumab therapy [182]. Analysis of the GRALQ scores after 24 weeks of mepolizumab therapy, showed an extra 10% increase from the baseline of the

proportion of patients rating their activity as “not” or “slightly” limited with mepolizumab versus placebo. GICALQ scores showed that 76% (versus 54% of patients in the placebo arm) rated their activity as “much better,” “better,” or “slightly better” since the start of the study with mepolizumab. [191].

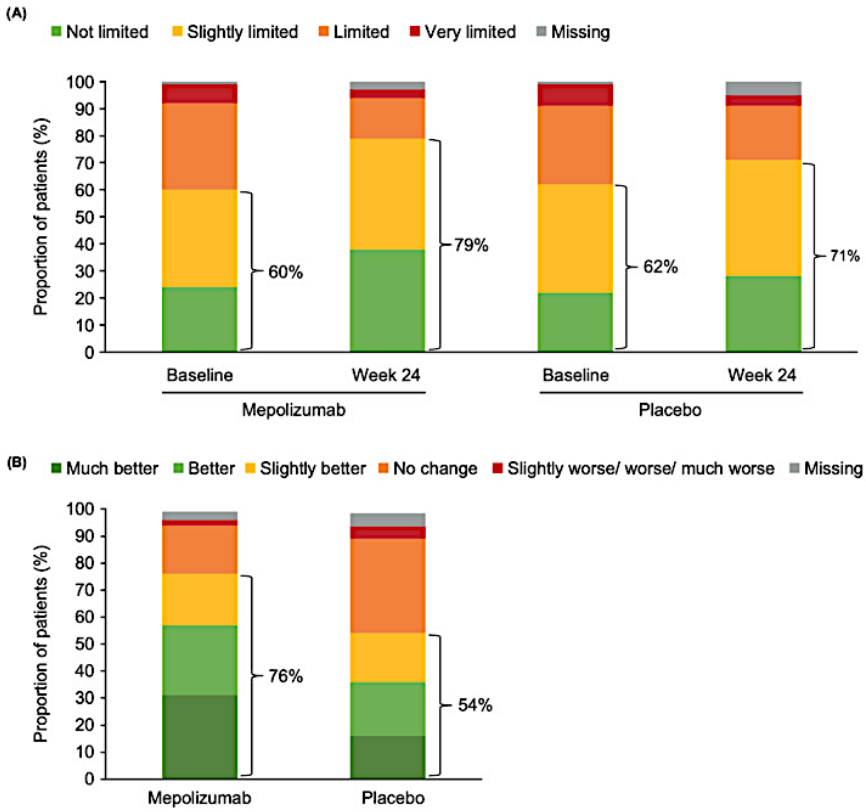


Figure 1: Activity limitation with mepolizumab versus placebo, as measured in (A) the Global Rating of Activity Limitation questionnaire at baseline and Week 24 of the MUSCA study, and (B) the Global Impression of Change in Activity Limitation questionnaire from the start of the study to Week 24 for 532 (269 in the mepolizumab arm; 263 in the placebo arm) patients who completed the MUSCA study (From [191]).

2.3 MONITORING of PHYSICAL ACTIVITY in DAILY LIFE

Physical activity was captured using a commercially available triaxial trunk accelerometer (DynaPort MoveMonitor; McRoberts B.V., The Hague, The Netherlands; FDA registered and CE marked). Specific software (DynaportManager, McRoberts B.V.)-generated reports were used to read the collected data (Figure 3 and 4). The MoveMonitor device has been extensively validated and used for activity detection and energy expenditure estimation in younger as well as older healthy populations and in chronic obstructive pulmonary disease (COPD), in both ordinary and sedentary conditions [192-197].

The MoveMonitor has a sample frequency of 100 samples/s and a range of -6 g to + 6 g. In general, this algorithm first determines whether the accelerometer was worn based on threshold and frequency analysis of the raw signal, and subsequently differentiates between inactive (lying and sitting), static (standing and shuffling) and moving (walking, stair walking and cycling) activities. As summarized elsewhere [198], validation studies report accuracies of 88% for non-wearing and accuracies of 86–99% for walking, 89% for cycling, 88–97% for standing, 91–99% for sitting, and 97% for lying.

The subjects were trained in the use of and equipped with accelerometers to record the intensity of their PADL. The accelerometers were attached to an elastic strap and mounted on the subjects' back, at the level of the L2 vertebra (an approximation of the body's center of mass) to wear for seven consecutive days. The subjects were advised to wear the accelerometer at all times (including sleep) for seven consecutive days excluding only aquatic activities such as showering,

bathing and swimming since this would damage the device. Data of days on which the accelerometer was worn more than 75% of the time (≥18 hours), were averaged to determine habitual type of daily activity; a minimum of 5 valid wearing days was required for a participant's data to be included in the analysis [199].

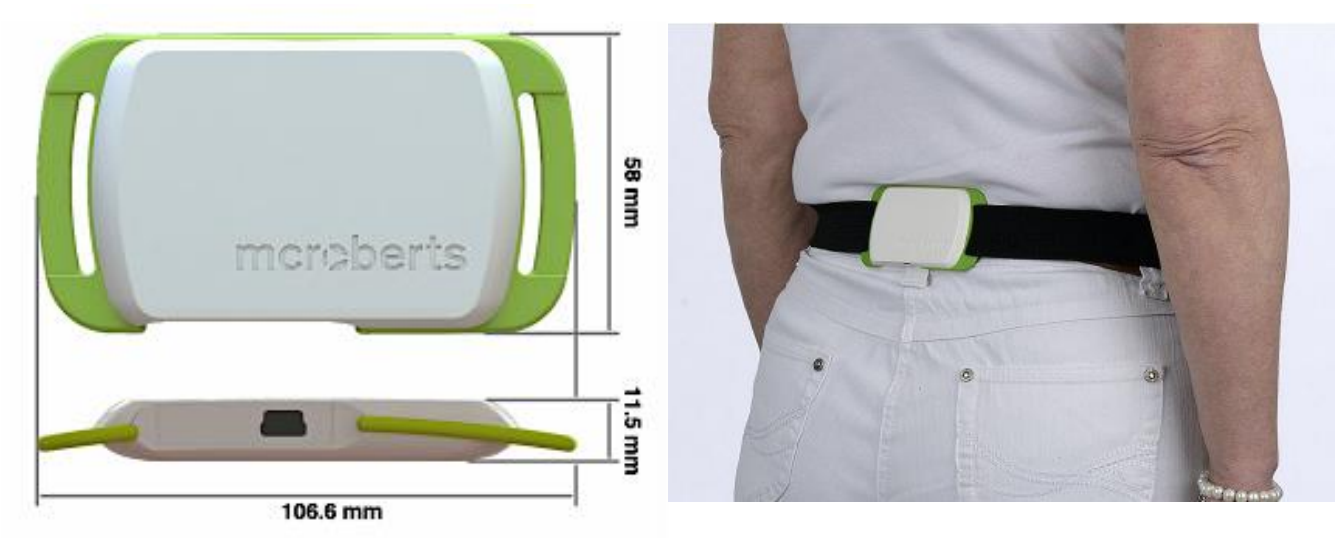


Figure 2: DynaPort MoveMonitor; McRoberts B.V., The Hague, The Netherlands (106.6x58x11.5mm, 55 grams; range ± 6 g, sampling frequency: 100Hz) and its positioning at the level of the L2 vertebra.

2.4 MEASURED PARAMETERS of PHYSICAL ACTIVITY

The studied parameters of PADL included daily step count, daily time spent in moderate-to-vigorous physical activity (MVPA; ≥3 METs) (min), daily MVPA volume (MET·min), daily Movement Intensity (MI; m/s^2; $9.81 m/s^2$ = 1 unit of gravitational acceleration g) and moving time (min), as provided by the algorithm for all whole-body moving activities (walking, stair walking and cycling). We calculated the daily time spent in MVPA by summing the time in moderate physical activity (3-5.9 METs) and the time in vigorous physical activity (≥6 METs) [3, 11]. In order to compare against guidelines for physical activity [3], we calculated the weekly time in moderate activity, weekly time in vigorous activity and weekly MET·min count from the daily data. In light of new evidence and guidelines [3, 23, 28, 29], bouts of any duration were considered for all the activities.

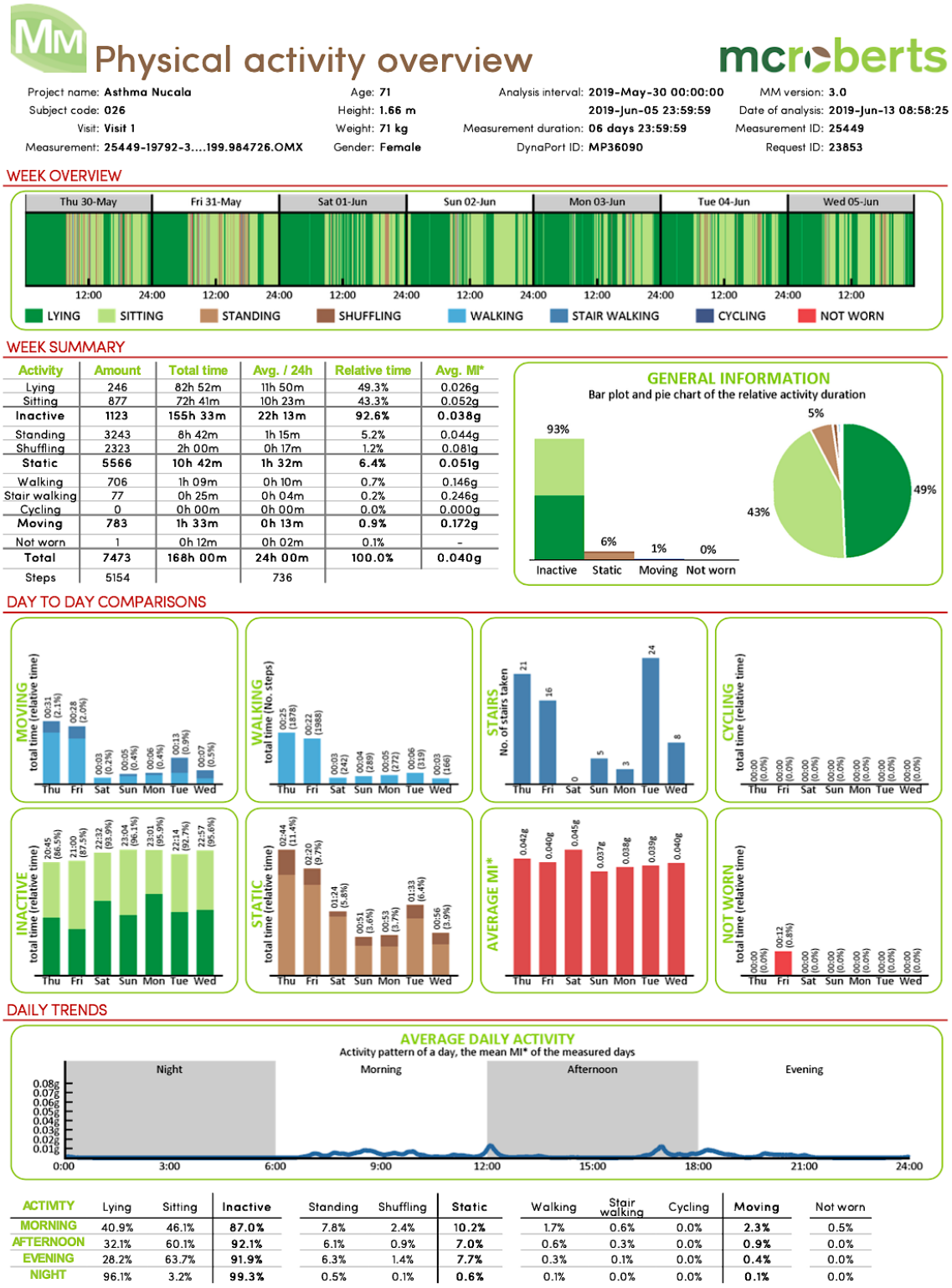
Steps are a basic unit of locomotion and as such, provide an intuitive, easy-to-understand and easy-to-measure metric of human ambulation and a crude representation of the overall physical activity. Steps can be at light-, moderate-, and vigorous-intensity levels, providing a range of exertion choice to promote walking at all ages and for all levels of fitness in the context of physical activity monitoring and prescription [20, 200]. Steps are also motivational and they facilitate behavior change. For these reasons, the measure of steps per day has the potential to improve the translation of research findings into public health recommendations, policies, and programs [200]. Daily step count has also strong associations with physical health variables. In severe asthma, daily step count has been associated with dyspnea, 6MWD, FEV_1, sputum eosinophils%, high-sensitivity CRP [62], and HRQoL [59]. However, patients with asthma do not always achieve satisfactory

levels of steps per day, have lower steps per day than healthy subjects and have declining daily step count with worsening disease status [58, 60, 73, 186].

The intensity with which subjects carry out physical activity is an important aspect of physical activity behavior that people adopt in daily living and a fundamental part of recommendations for health maintenance [3]. In this study, the daily intensity of bodily movement was measured in units of gravitational acceleration (g), expressed in meters per square second (m/s^2; $1g = 9.81 m/s^2$) and metabolic equivalents (METs). Using predefined METs criteria [11], the accelerometer algorithm classified physical activity into sedentary (<1.5 METs), light (1.5-2.9 METs), moderate (3-5.9 METs) and vigorous (≥6 METs). Moderate and vigorous physical activity were collectively considered as moderate-to-vigorous physical activity (MVPA; ≥3 METs). By combining the MET value of the activity with the activity duration (in minutes) the algorithm quantified MVPA in MET·min counts.

In asthma, time in MVPA was positively associated with disease control and disease-specific HRQoL [51, 59] and a 25-minute increase in MVPA was associated with a clinically significant improvement in ACQ score of 0.52 units [51]. However, the overall evidence is inconsistent as the raw values of time spent in MVPA by both asthma and healthy populations varies substantially between studies [201]. Also, time spent in MVPA was not significantly different between asthma and healthy subjects, once adjusting for confounding factors such age, sex, obesity and smoking [60].

The intensity of movement activity in m/s^2 represents a direct measure of the power of the movements. As such, it has been extensively investigated in COPD where it was shown to be an important aspect of PADL [202]. The movement intensity in patients with COPD has been reported in the range of 1.5 to 1.9 m/s^2, depending on the disease severity and study population [202-205]. Movement activity in m/s^2 has also been shown to be responsive to both pharmacological and exercise training interventions for promoting physical activity in people with COPD [206]. However, this measure of PADL has not been used in asthmatic patients to date.



Activity	Amount	Total time	Avg. / 24h	Relative time	Avg. MI*
Lying	246	82h 52m	11h 50m	49.3%	0.026g
Sitting	877	72h 41m	10h 23m	43.3%	0.052g
Inactive	**1123**	**155h 33m**	**22h 13m**	**92.6%**	**0.038g**
Standing	3243	8h 42m	1h 15m	5.2%	0.044g
Shuffling	2323	2h 00m	0h 17m	1.2%	0.081g
Static	**5566**	**10h 42m**	**1h 32m**	**6.4%**	**0.051g**
Walking	706	1h 09m	0h 10m	0.7%	0.146g
Stair walking	77	0h 25m	0h 04m	0.2%	0.246g
Cycling	0	0h 00m	0h 00m	0.0%	0.000g
Moving	**783**	**1h 33m**	**0h 13m**	**0.9%**	**0.172g**
Not worn	1	0h 12m	0h 02m	0.1%	-
Total	**7473**	**168h 00m**	**24h 00m**	**100.0%**	**0.040g**
Steps	5154		736		

ACTIVITY	Lying	Sitting	Inactive	Standing	Shuffling	Static	Walking	Stair walking	Cycling	Moving	Not worn
MORNING	40.9%	46.1%	**87.0%**	7.8%	2.4%	**10.2%**	1.7%	0.6%	0.0%	**2.3%**	0.5%
AFTERNOON	32.1%	60.1%	**92.1%**	6.1%	0.9%	**7.0%**	0.6%	0.3%	0.0%	**0.9%**	0.0%
EVENING	28.2%	63.7%	**91.9%**	6.3%	1.4%	**7.7%**	0.3%	0.1%	0.0%	**0.4%**	0.0%
NIGHT	96.1%	3.2%	**99.3%**	0.5%	0.1%	**0.6%**	0.1%	0.0%	0.0%	**0.1%**	0.0%

Figure 3: MoveMonitor report template for the extraction of information on physical activity.

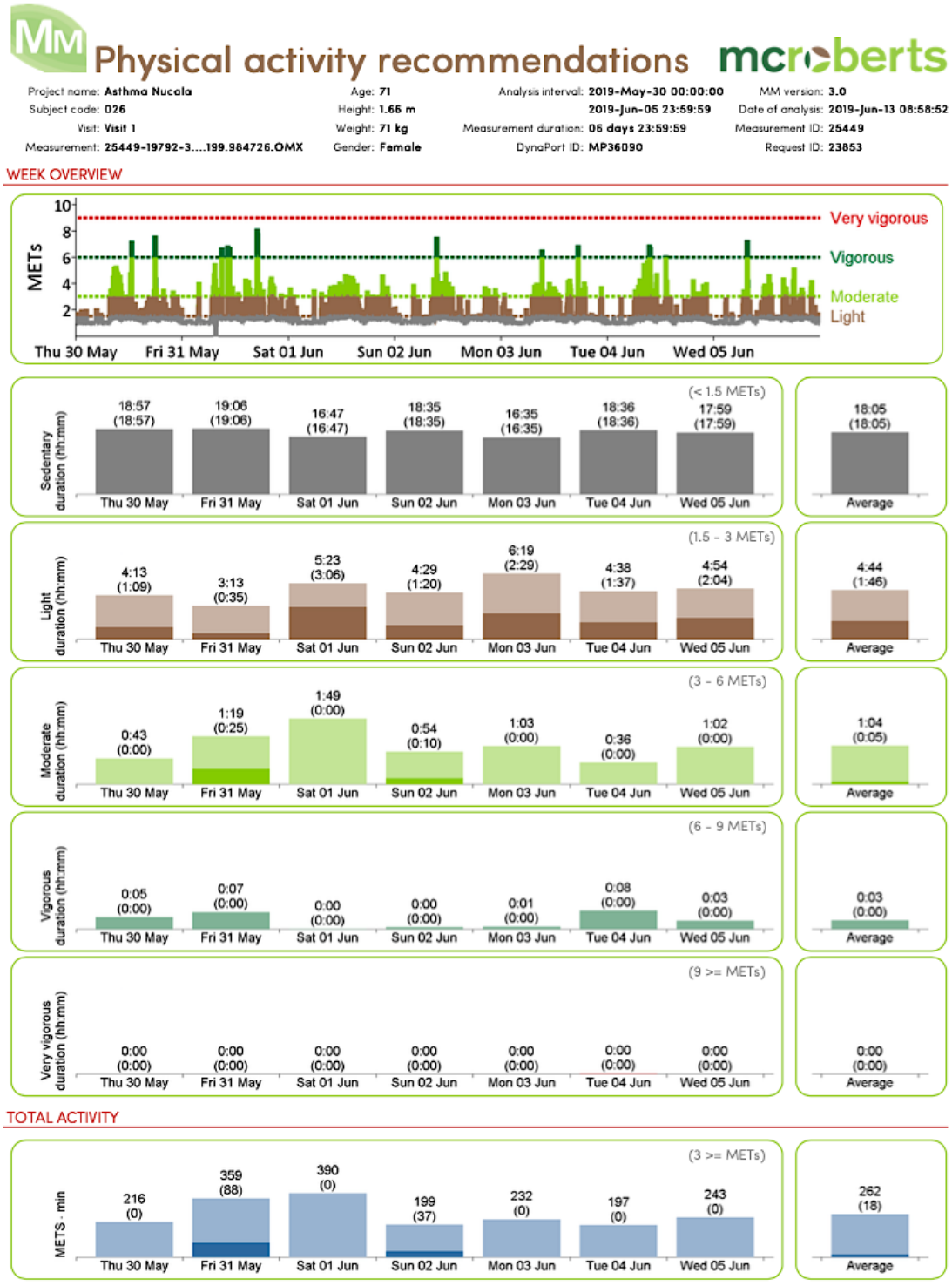


Figure 4: MoveMonitor report template for comparison of physical activity against recommendations.

2.5 PHYSICAL ACTIVITY GUIDELINES

The updated guidelines by the World Health Organization advise that adults should engage in at least 150-300 minutes of moderate-intensity (3-5.9 METs) aerobic physical activity throughout the week or do at least 75-150 minutes of vigorous-intensity (≥6 METs) aerobic physical activity throughout the week or an equivalent combination of moderate-and vigorous-intensity activity (MVPA; ≥3 METs), preferably spread evenly over 4 to 5 days a week, or every day [3]. When combining moderate and vigorous intensity activity to meet the current recommendation, the minimum goal should be in the range of 600 to 1200 MET·min per week [3, 19]. In light of new evidence [23, 28, 29], the updated guidelines take into consideration activity of any bout duration [3]. These recommendations are relevant to all healthy adults aged 18 and older (including aged 65 and older), irrespective of gender, race, cultural background or socioeconomic status. They are also relevant to people of all abilities including people with chronic non communicable medical conditions not related to mobility and are therefore applicable to patients with asthma. For a complete review of the guidelines please refer to the General Part I, page 14.

2.6 MEPOLIZUMAB BIOLOGIC THERAPY

Biologic medicines, produced by or derived from living organisms or their products, have revolutionized the practice of medicines that treat cancer, autoimmune and inflammatory diseases. In asthma, recent years have seen a surge in the study and use of therapeutic monoclonal antibodies; a new generation targeted biological medicines that selectively block pro-inflammatory antibodies, molecules, or cell receptors thus disrupting inflammatory pathways implicated in the pathogenesis of asthma. In 2018, biologic therapies had been included in the step-by-step medication scheme of the Global Initiative for Asthma (GINA) guidelines and are becoming the new standard of care for patients with severe uncontrolled asthma due to their effectiveness in reduction in asthma exacerbation rates and use of oral corticosteroids (OCS) [207].

In 2005, Omalizumab, a recombinant humanized anti-IgE monoclonal antibody that targets IgE by using antibodies that block IgE from binding to its high-affinity receptor, became the first, and for a long time the only available biologic therapy for severe allergic asthma. Since 2015, five additional biologic therapies that target specific cytokines of the T2-high pathway have been approved for asthma for use in patients with severe eosinophilic asthma: mepolizumab (IL-5 inhibitor, approved 2015), benralizumab (IL-5 receptor antagonist; approved 2017), reslizumab (IL-5 antagonists; approved 2016), Tezepelumab (thymic stromal lymphopoietin blocker; approved 2021) and dupilumab (IL-4 inhibitor; approved 2018). More biologic therapies for asthma are in the pipeline.

Mepolizumab was first approved by the US Food and Drug Administration (FDA) and the European Commission (EC) for severe asthma in 2015. It is the first-in-class humanized, monoclonal antibody (IgG1 kappa) that targets IL-5 with high affinity and specificity. It is believed to work by preventing IL-5 from binding to its receptor mainly on the surface of eosinophils. By targeting IL-5, the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils, mepolizumab reduces blood eosinophils without completely depleting them. It is currently approved as add-on maintenance treatment of adult and pediatric patients aged 6 years and older with severe asthma and with an eosinophilic phenotype. It has been studied in over 3,000 patients in 21 clinical trials across a number of eosinophilic indications and is the only biologic with about 7 years of safety and efficacy data in severe eosinophilic asthma.

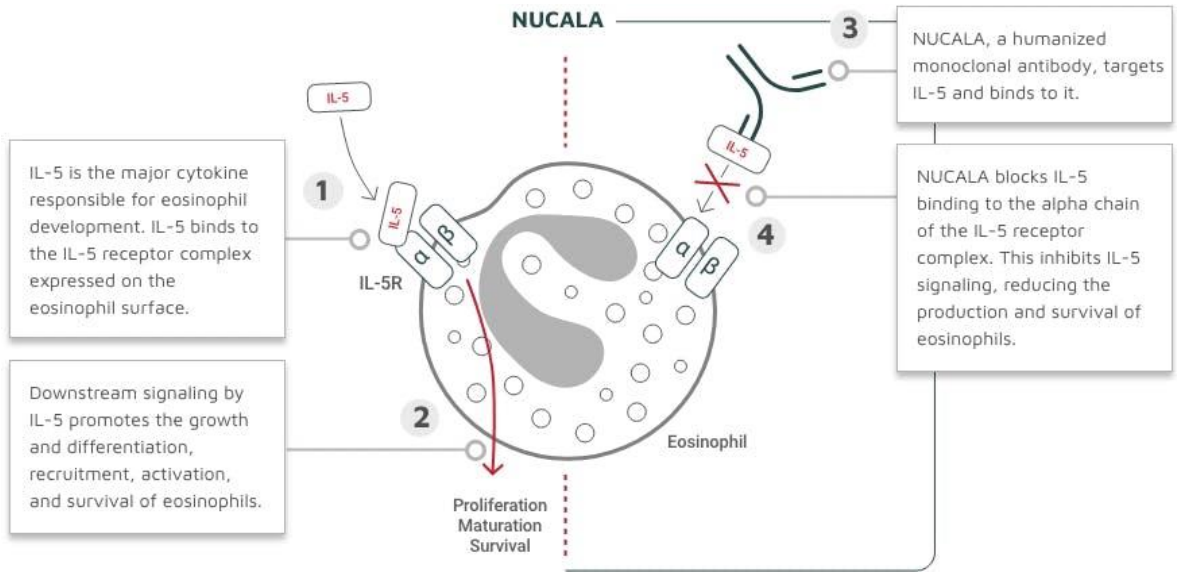


Figure 5: Mode of action of mepolizumab.

Mepolizumab therapy has been shown to lead to meaningful improvements in the use of OCS and asthma exacerbations but also, in asthma control and health-related quality of life. In phase-III trials, subcutaneous mepolizumab showed a significant 61%-68% reduction in rate of exacerbations requiring hospitalization/emergency department visits versus placebo [182, 208]. Confirmatory efficacy and safety data show a significant 50% reduction in median daily OCS dose during weeks 20-24 from baseline dose in patients treated with mepolizumab, compared to 0% reduction in patients treated with placebo ($p = 0.007$) [209]. Despite receiving a reduced glucocorticoid dose, patients in the mepolizumab group, as compared with those in the placebo group, had a relative reduction of 32% in the annualized rate of *all* exacerbations (1.44 versus 2.12) [209]. The beneficial effect of mepolizumab is maintained over time as evidenced by an up to 88% reduction in median OCS dose versus baseline at approximately 2.5 years (OCS dose at baseline, 11.3 mg/day versus 1.3 mg/day at week 128) [210] and 80% reduction in exacerbations at 3.6 years with mepolizumab versus pre-treatment (absolute rate/year reduction 4.04, n = 95) [210].

Mepolizumab has been additionally approved for the treatment for other diseases that are driven by eosinophilic inflammation and may coexist with asthma, including chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome. A post hoc meta-analysis suggests that mepolizumab led to an 80% reduction of exacerbations for patients with severe eosinophilic asthma and comorbid nasal polyps (rate ratio 0.2, 95% CI 0.11-0.35, n = 166) [211].

The magnitude to the mepolizumab effect in lung function appears less impressive. Historically, a minimal clinically important difference (MCID) of 100 mL has been proposed for FEV_1, although little evidence exists to support this value. However, in a study of 281 adult asthmatic patients, a minimal patient perceivable improvement for FEV_1, as determined by comparing the average baseline FEV_1 scores with patient global ratings of change in asthma, was 230 mL, or 10.38% change from baseline [212]. In phase-III trials the mean difference between mepolizumab and placebo for the change from baseline in pre-bronchodilator FEV_1 was 114 mL (95% CI, −42 to 271) at week 24 [209] and 98 mL (95% CI 11 to 184) at week 32 [208]. A phase-III trial also showed a treatment difference in FEV_1 of 120 mL (95% CI 47 –92) after 24 weeks of mepolizumab therapy compared with placebo [182]. A post hoc meta-analysis of two phase-III trials [182, 208], confirmed an increase from baseline in FEV_1 with mepolizumab therapy (n = 449) compared with placebo (n = 438) after 24 or 32 weeks (treatment difference 111 mL; 95% CI 55 – 166) [213]. Mepolizumab was also associated with attenuated lung function decline over the course of 12 months in severe eosinophilic asthma patients from the Belgian Severe Asthma Registry [214]. Finally, a retrospective observational real-life study of adult patients (n = 105) showed improvements in small airway function after 18 months of mepolizumab therapy, as evidenced by a highly significant, gradual and persistent increase in FEF 25-75% values (from 32.7 ± 18.2% at baseline to 48.6 ± 18.4%) [215].

Evidence shows meaningful improvements with mepolizumab compared to placebo in asthma control/symptom burden (mean difference in ACQ-5 score of

0.52 points (95% CI, −0.87 to −0.17) and HRQoL (mean difference in SGRQ total score ranging -7.4; 95% CI -9.5 to -5.3; [213] to −5.8; 95% CI, −10.6 to −1.0 [209]). The proportions of patients achieving the MCID from baseline in SGRQ total score as well as ACQ-5 score were also higher with mepolizumab compared with placebo (58% versus 41% [209], 72% versus 55% [213] and 71% versus 55% [214] for SGRQ total score; and 58% versus 44% for ACQ-5 score [213]).

The patients in the mepolizumab arm of the current study received the recommended dose 100 mg of mepolizumab (Nucala; GlaxoSmithKline, London, UK) administered once every four weeks for 12 months by subcutaneous injection into the upper arm. The patients had their therapy prepared and administered by a respiratory physician in a hospital environment. We used Nucala for injection supplied in the form of sterile, preservative-free, white to off-white, lyophilized powder in 100-mg single-dose vials with a flip-off seal in cartons of 1. As per the explicit dosing and administration instructions [216]. Nucala was reconstituted in the vial with 1.2 mL of Sterile Water for Injection, using a 2- or 3-mL syringe and a 21-gauge needle. The stream of Sterile Water for Injection was directed vertically onto the center of the lyophilized powder. The vial was gently swirled for 10 seconds with a circular motion at 15-second intervals until the powder was dissolved. Reconstitution was typically completed within 5 minutes after the Sterile Water for Injection was added. The reconstituted solution contained a concentration of 100 mg/mL mepolizumab. Before injection, the reconstituted solution was visually inspected for particulate matter and clarity before use.

Figure 6: Nucala vial.

The safety of Nucala was evaluated in numerous studies, including a 4.5-year open-label study [217]. In 3 clinical trials, the percentages of subjects who experienced systemic (allergic and nonallergic) reactions were 3% for Nucala and 5% for placebo. The most common side effects of Nucala include headache, injection site reactions (pain, redness, swelling, itching, or a burning feeling at the injection site), back pain, and fatigue. A majority of the systemic reactions were experienced on the day of dosing. Approximately 2% of patients receiving Nucala vs 3% receiving placebo withdrew due to adverse events [218]. Across clinical trials in patients aged ≥6 years receiving Nucala, 6% developed anti-mepolizumab antibodies and 1 patient had neutralizing antibodies detected. The clinical relevance of anti-mepolizumab antibodies is not known [218].

In the current study, patients were monitored for 15 minutes after administration of the biologic agents for any immediate allergic (hypersensitivity) reactions, including anaphylaxis and provided with guidance in the event of late allergic relations. Patients were also monitored for adverse effects throughout the study.

2.7 STATISTICAL ANALYSIS

Data were analyzed using the SPSS statistical package v28.0. Normal distribution of the data was checked using the Shapiro-Wilk test. Data are expressed as mean ± standard deviation or median (interquartile range) for continuous outcomes, and as counts and percentages for categorical variables. Independent samples t-tests or Mann–Whitney U-tests were used for comparisons of differences in clinical characteristics and PADL parameters (daily step count, time in MVPA, MVPA volume, MI and moving time) between patients with mild-to-moderate asthma and patients with severe asthma. Chi-square tests were used for detection of between-group differences in compliance with guideline recommendations. Associations of PADL parameters with FEV_1, ACT score and SGRQ score as well as associations between all of the PADL parameters were examined using Pearson's or Spearman's correlation coefficient, depending on the distribution of the data. Paired samples t-tests or Wilcoxon signed rank tests were used to examine for changes with therapy in PADL parameters, FEV_1, ACT score, SGRQ score and eosinophil count. The level of significance was set at $p < 0.05$.

3. RESULTS

3.1 STUDY FLOW

A total of 38 patients were enrolled between January 2018 and March 2020. The study was prematurely concluded due to the advent and persistence of the coronavirus disease 2019 (COVID-19) pandemic in Greece. The decision was made for health and safety reasons but also due to the prolonged public mobility restrictions and lockdowns imposed at a national and global level, which could introduce a systematic error (bias). Two patients (6%) with mild-to-moderate asthma were excluded due to poor wearing compliance. Thirty-six patients were therefore considered in the analysis for the physical activity arm of the study of whom, 15 had mild-to-moderate asthma and 21 had severe asthma. Sixteen of the patients with severe asthma had eosinophilic asthma and commenced on mepolizumab therapy. Twelve patients completed successfully 12-month therapy and included in the analysis for the mepolizumab study arm; 2 patients dropped out due to worsening of asthma symptoms and 2 patients were excluded for not following the instructed medication. The study entry PADL data of the 4 excluded patients from the mepolizumab arm, were still used for the physical activity arm. The study flow is shown in Figure 7.

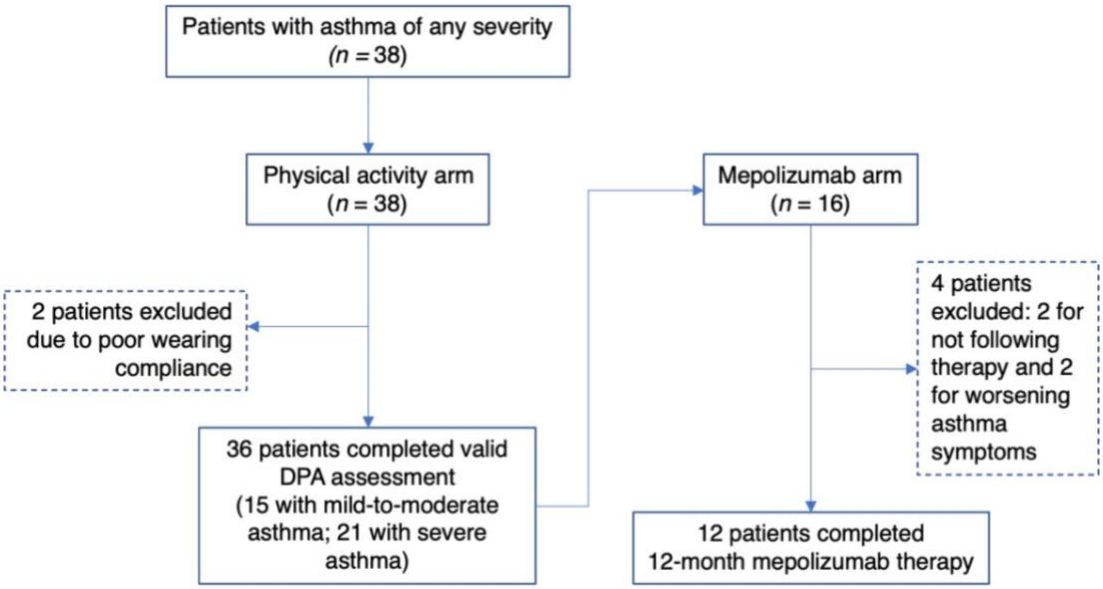


Figure 7: Study flowchart. PADL: physical activity in daily life.

The outcome in the present study is not dissimilar from a real-world study of 368 patients with severe asthma [219], where 19% of patients discontinued mepolizumab therapy during 1 year of treatment, the most common reasons being participant decision (7%) and patient-reported lack of efficacy (4%) [219]. Treatment-emergent adverse events occurred in 14% of patients, and they led to discontinuation of therapy in 2%; serious but not-fatal adverse events occurred in < 1% of patients [219].

Of note, sporadic, paradoxical worsening of asthma symptoms and lung function with mepolizumab therapy has been reported [220, 221]. It is hypothesized to be due to local autoimmune reactions with anti-IL-5 monoclonal antibodies forming immune complexes with IL-5 cytokines, which prevents degradation of IL-5 and leads to further excessive airway inflammation [221]. This mechanism may be mediating the increase in IL-5 after the initiation of mepolizumab treatment

compared with the baseline values that has been observed in several studies; other possible causes include increased IL-5 receptor expression, and/or increased T helper cells that produce intracellular IL-5 [222].

3.2 PATIENT CHARACTERISTICS

Patients were 29 females (81%) and 7 (19%) males with mean age 49.8 ± 14.8 years, body mass index (BMI) 29.2 ± 6.8 kg/m^2, FEV_1 83.4 ± 26.4% predicted, FEV_1 to FVC ratio 0.74 ± 0.15. All of the patients were on regular therapy with at least a combination of inhaled corticosteroid and long-acting beta agonist. ACT score was 19.1 ± 5.4, and SGRQ score 36.8 ± 25.5. There was no difference in age, sex, and BMI between patients with mild-to-moderate asthma and severe asthma but patients with severe asthma had lower FEV_1 ($p = 0.001$), ACT score ($p<0.001$) and SGRQ score ($p<0.001$). The patients' complete characteristics are shown in Table 1.

	All (n = 36)	**Mild-to-Moderate Asthma (n = 15)**	**Severe Asthma (n = 21)**	***p***
Sex, F/M	29/7	11/4	18/3	0.362
Age	49.8 ± 14.8	45.1 ± 16.5	53.1 ± 12.8	0.172
BMI (Kg/m^2)	29.3 ± 6.8	27.7 ± 4.6	30.3 ± 7.9	0.238
FEV_1 (L)	2.4 ± 1.1	3.1 ± 1.17	1.9 ± 0.8	<0.001
FEV_1% predicted	83.4 ± 26.4	96.1 ± 19.2	73.9 ± 27.4	0.006
FEV_1/FVC ratio	0.74 ± 1.5	0.79 ± 0.1	0.70 ± 0.2	0.084
Therapy				
ICS/LABA	36	15	21	N/A
LAMA	20	1	19	N/A
Montelukast	22	7	15	N/A
OCS	2	0	2	N/A
Omalizumab	2	0	2	N/A
ACT score	20 (9)	25 (4)	15 (5)	<0.001
SGRQ score	30.8 (44.1)	58.8 (34.5)	12.6 (10.8)	<0.001

Table 1. Patient characteristics. Data are presented as the mean ± SD, median (interquartile range) or counts. FEV_1: prebronchodilator forced expiratory volume in 1 second; FVC: prebronchodilator forced vital capacity; ICS: inhaled corticosteroids, OCS: oral corticosteroids; LABA: long-acting beta agonist; LAMA: long-acting muscarinic agonist; ACT: Asthma Control Test; SGRQ: St George Respiratory Questionnaire; N/A: not applicable or not assessed.

3.3 PHYSICAL ACTIVITY in DAILY LIFE

For the whole cohort, daily step count was 7,806 ± 3,823 steps; time in MVPA 123 (interquartile range, 63) min, MVPA volume 576 ± 256 MET·min, MI 1.96 (0.45) m/s^2 and moving time 94 ± 43 min. As shown in Table 2, despite large mean differences (MD) in favor of the patients with mild-to-moderate asthma compared to the patients with severe asthma, the between-group differences were not statistically significant.

For the whole patient cohort, there were significant associations between PADL and FEV_1 (r for step count = 0.40, p = 0.018; r for time in MVPA time = 0.36, p = 0.036; r for MVPA volume = 0.42, p = 0.012; r for MI = 0.44, p = 0.008). Daily MI (but not any of the other PADL parameters) associated with ACT score (r= 0.37, p = 0.027). There were no associations between any PADL parameter and SGRQ score (r= 0.30–0.33, p = 0.052–0.090 for all). There were strong associations between daily step count, time in MVPA, MVPA volume and MI and moving time (r = 0.50–0.96, p = 0.003-0.001 for all).

	All (n = 36)	**Mild-to-moderate asthma** (n = 15)	**Severe asthma** (n = 21)	***p***
Daily step count	7806 ± 3823	8209 ± 3815	7518 ± 3896	0.558
Daily Movement Intensity (m/s^2)	1.96 (0.45)	2.09 (0.46)	1.72 (0.50)	0.083
Daily time in MVPA (min)	123 (63)	133 (64)	97 (70)	0.505
Daily MVPA volume (MET·min)	657 ± 255	618 ± 244	547 ± 266	0.553
Daily moving time (min)	94 ± 43	98 ± 44	91 ± 43	0.630
Patients met recommendations for weekly time in moderate activity [min/week] [3].	36; 100% [745 (392)]	15; 100% [742 (357)]	21; 100% [777 (389)]	1
Patients met recommendations for weekly time in vigorous activity [min/week] [3].	15; 41% [70 (137)]	8; 53% [126 (168)]	8; 38% [28 (112)]	0.464
Patients met recommendations for weekly MVPA volume [MET·min] [3, 19].	36; 100% [4034 ± 1791]	15; 100% [4323 ± 1707]	21; 100% [3828 ± 2651]	1

Table 2: Physical activity in daily life and comparison against current guidelines. Data are presented as the mean ± SD, median (interquartile range) or counts and percentages. MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent.

3.4 COMPLIANCE with PHYSICAL ACTIVITY GUIDELINES

The percentage of all patients who met current recommendations for moderate, vigorous or combined moderate and vigorous daily physical activity, was 100%, 42% and 100%, respectively. Only 38% of patients with severe asthma met the recommendations for weekly time in vigorous activity. There were no significant between-group differences (Table 2).

3.5 THE EFFECT OF MEPOLIZUMAB THERAPY

After 12-month therapy, the 12 patients (10 female; age 57.4 ± 8.7 years; BMI 29.8 ± 3.5 Kg/m^2, FEV_1% pred. 68.6 ± 26.5; ACT score 15 (5); SGRQ score 58.8 (34.5) on the mepolizumab arm showed significant improvement in all the aspects of PADL. Daily step count increased from 7,233 ± 3,994 to 7,879 ± 3,892 steps (MD 646; 9%), p = 0.009), daily time in MVPA increased from 97 (70) to 117 (64) min (MD 20; 21%), p =0.003), daily MVPA volume increased from 519 ± 164 to 606 ± 269 MET·min (MD 87; 17%), p<0.001) and MI increased from 1.72 (0.50) to 1.83 (0.48) m/s^2 (MD 0.11; 6%), p = 0.003) (Figure 8). There was no change in daily moving time before and after therapy (87 ± 43 versus 89 ± 34 min; p = 0.906).

Patients also exhibited meaningful improvement in FEV_1 (from 1.74 ± 0.8 to 1.88 ± 0.8, p = 0.004), ACT score (from 15.73 ± 4. to 21.1 ± 4.8, p = 0.003) [190] and SGRQ score (from 52.3 ± 20.7 to 30.6 ± 21.9, p = 0.004) [189]. There was no association between mean changes in the four PADL parameters and mean change in FEV_1 (p>0.1 for all). Finally, there was significant change in the self-reported GICALQ with all the patients rating their physical activity as “much better (25%)”, “better (50%)” or “slightly better (25%)” than prior to therapy. In GRALQ, the proportion of patients rating their activity as “not limited” or “slightly limited” increased from 25% to 75% (Figure 9). The individual responses in GRALQ and GICALQ are shown in Table 4 and 5, respectively. As expected, after 12 months of mepolizumab therapy, the eosinophil count was reduced (from to 5.6 ± 2.6 to 1.2 ± 0.6, p < 0.001), but not eliminated.

	PRE-therapy (n = 12)	**POST-therapy** (n = 12)	***p***
Daily moving time (min)	87.4 ± 42.8	88.6 ± 34.4	0.906
Daily steps	7233 ± 3994	7879 ± 3892	0.009
Moving Intensity (m/s^2)	1.91 ± 0.35	2.1 ± 0.36	0.002
Daily time in MVPA (min)	109 ± 50.3	125.8 ± 50.7	0.002
Daily MVPA volume (3≥MET·min)	519 ± 164	606 ± 269	<0.001
FEV_1	1.74 ± 0.8	1.88 ± 0.8	0.004
FEV_1% predicted	67.8 ± 27.8	76.1 ± 26.9	<0.001
GRAL score	1.91 ± 0.9	0.91 ± 0.8	0.002
ACT score	15.73 ± 4.3	21.1 ± 4.8	0.003
SGRQ score	52.3 ± 20.7	30.6 ± 21.9	0.004
Eosinophil count	428.1 ± 179.5	104 ± 54.5	<0.001
Eosinophils%	5.6 ± 2.6	1.2 ± 0.6	<0.001

Table 3 : The effect of mepolizumab therapy. Data are presented as the mean ± SD or median (interquartile range). MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent.

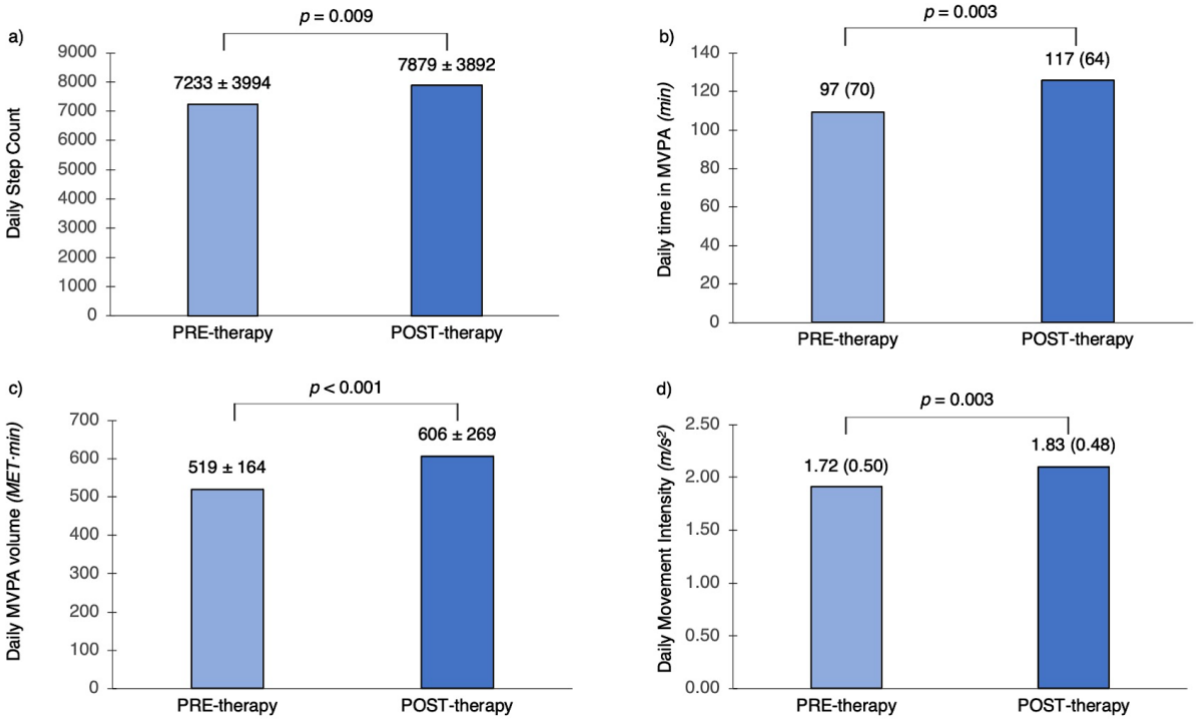


Figure 8: Changes in physical activity in daily life with mepolizumab therapy. Data are presented as the mean ± SD or median (interquartile range). MVPA: moderate-to-vigorous physical activity; MET: metabolic equivalent.

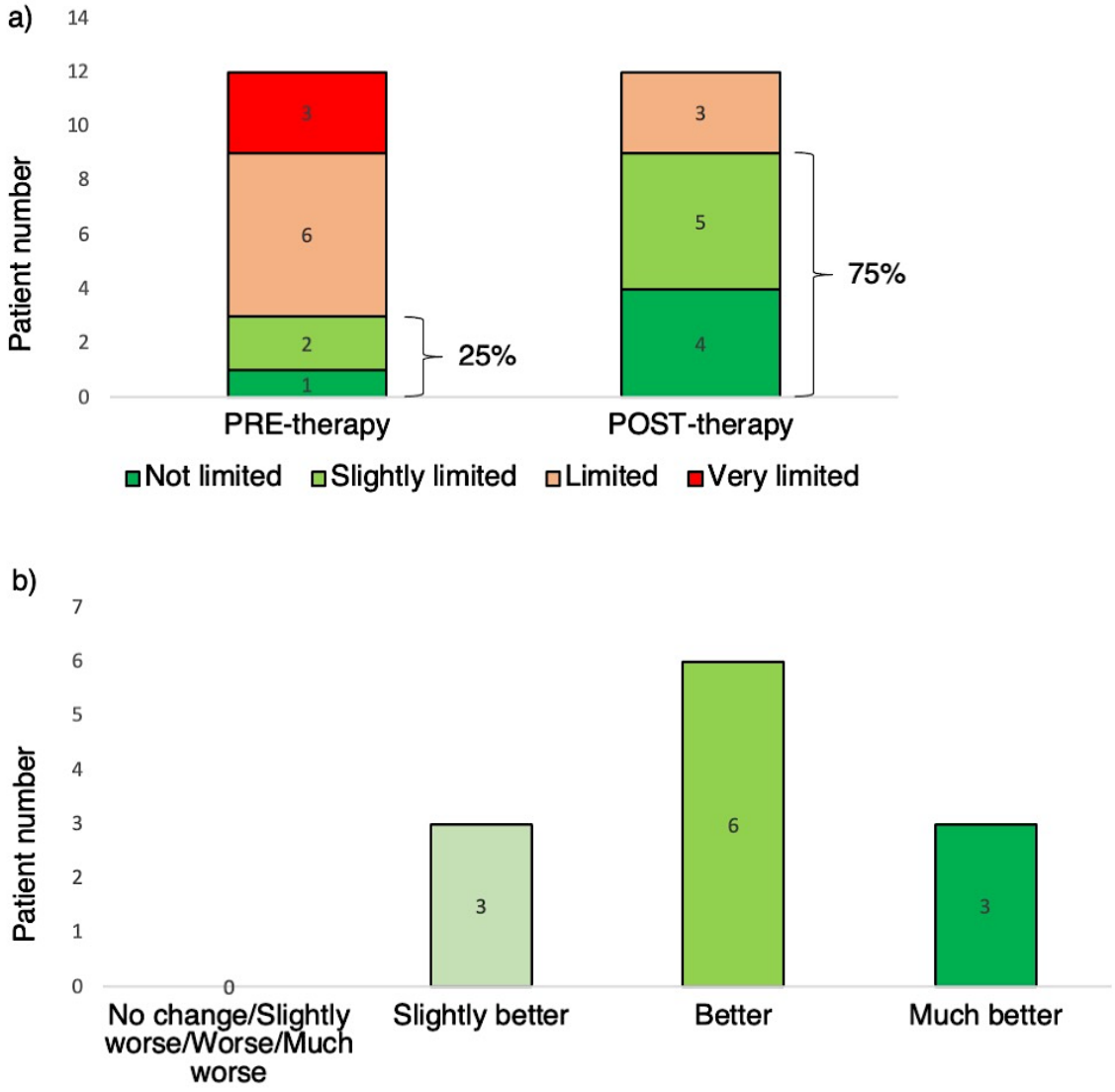


Figure 9: a) Global Rating of Activity Limitation before and after mepolizumab therapy; b) Global Impression of Change in Activity Limitation after mepolizumab therapy.

Patients	**Not limited**	**Slightly limited**	**Limited**	**Very limited**
1	X	X		
2		X	X	
3		X	X	
4			X	X
5			X	X
6	X			X
7		X	X	
8		X	X	
9		X	X	
10	X X			
11			X X	
12	X	X		

Table 4: Individual responses in Global Rating of Activity Limitation questionnaire before and after mepolizumab therapy. **X**: Pre-mepolizumab therapy**;** X: Post-12-month mepolizumab therapy.

Patients	**Much worse**	**Worse**	**Slightly worse**	**No change**	**Slightly better**	**Better**	**Much better**
1						X	
2							X
3						X	
4					X		
5					X		
6							X
7						X	
8						X	
9						X	
10					X		
11						X	
12							X

Table 5: Individual responses in the Global Impression of Change in Activity Limitation questionnaire after 12-month mepolizumab therapy.

4. DISCUSSION

In this study of patients with moderate-to-severe and severe asthma, the levels of PADL are deemed borderline satisfactory. All the patients met at least one recommendation for PADL but less than half met recommendations for vigorous PADL and there was space for improvement in all the aspects of PADL, especially for patients with severe asthma. Importantly, in a non-sedentary cohort of older patients with severe asthma, mepolizumab increased meaningfully daily step count by 646 steps (9%), time in MVPA by 20 min (20%), MVPA volume by 87 MET·min (17%) and MI by 0.11 m/s^2 (6%). This accelerometer-derived improvement matched self-reported improvement in PADL. Clinically significant improvements also occurred for lung function, asthma control and HRQoL.

Individually, all the patients met at least one of the recommended thresholds for moderate activity, vigorous activity or an equivalent combination of MVPA [3]. However, the absolute compliance with recommendations was driven by performance in moderate-intensity physical activity rather than in vigorous physical activity (VPA). VPA compliance for all patients, mild-to-moderate asthmatics and severe asthmatics was 41%, 53% and 38%, respectively with some individuals showing negligible or absent VPA. This is important since VPA is an indispensable aspect of PADL. In a national cohort study of 403,681 adults, VPA showed a stronger inverse association with cancer mortality compared with moderate physical activity. Also, among participants performing any MVPA, a higher proportion of VPA to total physical activity was associated with lower all-cause mortality, across sociodemographic characteristics, lifestyle risk factors, and chronic conditions at baseline [26].

In terms of the weekly MVPA volume, the performance of our patients (3828 ± 2651 MET·min/week for severe asthmatics and 4323 ± 1707 MET·min/week for moderate-to-severe asthmatics) may seem in excess in relation to the recommended range of 600 to 1,200 MET·min/week [3, 19]. However, recommendations refer merely to the minimal required amount of activity in order to achieve substantial benefits over and above the routine light-intensity activities of daily living. Strong evidence suggests that total physical activity needs to be several times higher (≥ 3,000—4,000 MET·min/week), than the recommended minimum level to achieve significant health benefits such as reducing the risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events [25].

The daily step count was 7,806 ± 3,823 steps for the total cohort, 8,209 ± 3,815 steps for patients with mild-to-moderate asthma, and 7518 ± 3896 steps for patients with severe asthma. There are still no evidence-based public health guidelines recommending a range for steps per day for health benefits to cross-reference our data against. However, the patients with severe asthma only reached the threshold of the “somewhat active” category (7,500–9,999 steps per day) in a widely endorsed step-defined ladder of physical activity [31, 53]. Crucially, most of the patients were not shown to gain full potential of benefit from their daily step count [5]. Robust evidence shows that increasing daily step count is associated with progressively lower mortality risk, with the risk plateauing for older adults (aged ≥60 years) at approximately 6,000–8,000 steps per day and for younger adults (aged <60 years) at approximately 8,000–10,000 steps per day [5], but only 55% of our study population walked within these ranges.

The observed increase in PADL with mepolizumab therapy is meaningful as it translates directly to clinical benefits and helps the patients to achieve beneficial goals for physical activity. Strong evidence shows that increments in daily step count as well as duration or frequency of MVPA are associated with a progressively lower risk of all-cause mortality [4, 23, 24, 223] and current recommendations are that additional physical activity of any bout duration and intensity, accumulated over the day and week, is beneficial [3, 21]. Importantly, the achieved mean increase of 646 steps per day with mepolizumab therapy matched the minimal important difference for first hospital admission in COPD patients due to an exacerbation after 3-month multidisciplinary pulmonary rehabilitation, estimated to be 600–1,000 steps per day [224]. It also surpassed the threshold of 500-step increment of steps per day shown to lower the risk of cardiovascular disease by 6%, and approached the 1,000-step increment of steps per day that was associated with a 23% decreased risk of all-cause mortality [223]. Interestingly, there was no concurrent change in daily moving time with mepolizumab, which means that patients achieved higher levels of PADL via increasing the intensity rather than the duration of their activities.

To our knowledge, the present is the second study to investigate the effect of any asthma therapy on PADL. Carpagnano et al. [172] found significant improvements in daily step count and energy expenditure in 30 patients treated with biological therapy (omalizumab or mepolizumab) for six months compared to patients on traditional therapy. The magnitude of improvement with biologic therapy was notably larger than in our study, as the patients almost doubled their daily steps (from 3,806 ± 421 to 6,545 ± 844) [39]. However, those patients were highly

sedentary compared to our patient cohort, which certainly allowed a larger space for improvement.

Herein, we provide the first data on MI in asthma expressed in acceleration units, being 1.96 (0.45) m/s2 for the total cohort. The MI in m/s2 represents a direct measure of the absolute power of movement. It has been extensively investigated in COPD, where it was shown to be an important aspect of PADL, ranging 1.5 to 1.9 m/s2 depending on the disease severity and study population [202-204] and responsive to pharmacological and exercise interventions [206]. With a mean MI of 1.72 (0.50) m/s^2, our patients with severe asthma showed similar performance to generally older patients with at least moderate COPD.

Finally, we observed modest associations of PADL with FEV_1. This is in line with the finding by Hennegrave et al. [61] that FEV_1 is associated modestly with daily step count in asthmatic patients. van't Hul et al. [66] and Bahmer at al. [60] found no associations between accelerometer-derived parameters of PADL and spirometric measures or peak expiratory flow rates in asthma, but daily step count was associated with impulse oscillometric airway resistance and small airway dysfunction [60].

A review of previous available studies on PADL in severe asthma patients is provided in Table 3. Notably, there is considerable variation in the levels of PADL among the studies, ranging from low sedentary to acceptably active. Possible causes include variations in cultural and behavioral patterns, seasonality as well as disparities in methodology and the way that data are presented. The type of the

device, wear location, speed and duration of movement can all affect the accuracy of measures obtained from different devices; counts obtained from different devices are highly correlated but can vary significantly [5]. Compared to four studies that used an arm-positioned accelerometer and two studies that used an above hip-positioned accelerometer, we used an accelerometer that is positioned on the back, at the level of the L2 vertebra, an approximation of the body's center of mass.

Study	**n**	**Accelerometer (position)**	**DSC**	**Daily time in MVPA**	**DSC associations**
Bahmer et al. [60]	63	SenseWear Pro Armband (upper arm)	6174 (4822–9277)	125 (68–172)	Impulse oscillometric airway resistance/ small airway dysfunction
Cordova-Rivera et al. [58]	61	ActiGraph wGT3X-BT (dominant hip)	5362 (3999–7817)	22 (13–38)	6MWD, ACT score, FEV_1, hs-CRP
Cordova-Rivera et al. [62]	62	ActiGraph wGT3X-BT (dominant hip)	5385 (3941–7844)	22 (13–35)	6MWD, FEV_1% pred., dyspnea, hs-CRP, eosinophils%
Carpagnano et al. [172]	40	SenseWear Pro Armband (upper arm)	3806 ± 421	N/A	N/A
Hennegrave et al. [61]	23	SenseWear Pro Armband (upper arm)	6560 ± 3915	120 ± 54	Age, anxiety, FEV_1
Neale et al. [59]	48	SenseWear Pro3 Armband (upper arm)	5183 ± 2935	12 ± 21	EQ-5D-3L, AQLQ score, CRQ score

Table 6. Studies on physical activity in daily life in severe asthma. Data are presented as Mean ± SD or median (interquartile range). DSC: daily step count; MVPA: moderate-to-vigorous physical activity; 6MWD: 6-minute walk distance; ACT: Asthma Control Test; FEV_1: forced expiratory volume in 1 second; hs-CRP: high-sensitivity C-reactive protein; AQLQ: Asthma Quality of Life Questionnaire; CRQ: Chronic Respiratory Disease Questionnaire.

The main limitation of the current study is the small sample size, which reduces the generalizability of results. As suggested by the large mean differences, significant between-group differences in PADL as well as significant associations of PADL may have been overlooked due to the inadequate statistical power. Another limitation is the absence of a control group for the mepolizumab arm to strengthen the results of the study. Our data is from a single center, but our patients are considered representative of a public referral center for asthma and severe asthma in Greece. Finally, the authors would like to acknowledge the negative impact of the COVID-19 pandemic, leading to the premature termination of the study as the public physical activity remains limited compared to the pre-pandemic era. Ongoing recommendations for physical distancing, quarantine measures for people with COVID-19, individual precautionary behaviors and fear of disease are leading to the adaptation of new habits that continue to bear a strong negative impact on day-to-day life physical activity and sedentary behavior worldwide [225, 226]. This is an unfortunate, important consideration for any current or future study in physical activity.

5. CONCLUSIONS

By showing meaningful improvements in several parameters of the PADL of patients with severe asthma with mepolizumab therapy, this study adds to the limited available evidence on the effect of biologic therapy on physical activity in asthma. Larger, multicenter studies are needed to validate our preliminary results, but the potential of a single, add-on intervention on improving such an important patient-centered and challenging outcome is appealing. For the multiple, significant general health and asthma-specific benefits of physical activity, PADL reflects long-established behavioral patterns that are often difficult to amend even when the disease severity and control improve. Longer-lasting interdisciplinary approaches targeting beyond asthma-specific endpoints may therefore be required to help patients meet recommendations and achieve their maximum potential in PADL and lifestyle pursuits. This is an important consideration not only for patients with severe asthma who plausibly draw the major share of interest, but for all the patients with asthma, who often present suboptimal levels of physical activity.

REFERENCES

1. Caspersen, C. J., K. E. Powell, and G. M. Christenson. "Physical Activity, Exercise, and Physical Fitness: Definitions and Distinctions for Health-Related Research." *Public Health Rep* 100, no. 2 (1985): 126-31.
2. Fleming, T. R., and J. H. Powers. "Biomarkers and Surrogate Endpoints in Clinical Trials." *Stat Med* 31, no. 25 (2012): 2973-84.
3. Bull, F. C., S. S. Al-Ansari, S. Biddle, K. Borodulin, M. P. Buman, G. Cardon, C. Carty, J. P. Chaput, S. Chastin, R. Chou, P. C. Dempsey, L. DiPietro, U. Ekelund, J. Firth, C. M. Friedenreich, L. Garcia, M. Gichu, R. Jago, P. T. Katzmarzyk, E. Lambert, M. Leitzmann, K. Milton, F. B. Ortega, C. Ranasinghe, E. Stamatakis, A. Tiedemann, R. P. Troiano, H. P. van der Ploeg, V. Wari, and J. F. Willumsen. "World Health Organization 2020 Guidelines on Physical Activity and Sedentary Behaviour." *Br J Sports Med* 54, no. 24 (2020): 1451-62.
4. Loprinzi, P. D., J. P. Loenneke, H. M. Ahmed, and M. J. Blaha. "Joint Effects of Objectively-Measured Sedentary Time and Physical Activity on All-Cause Mortality." *Prev Med* 90 (2016): 47-51.
5. Paluch, A. E., S. Bajpai, D. R. Bassett, M. R. Carnethon, U. Ekelund, K. R. Evenson, D. A. Galuska, B. J. Jefferis, W. E. Kraus, I. M. Lee, C. E. Matthews, J. D. Omura, A. V. Patel, C. F. Pieper, E. Rees-Punia, D. Dallmeier, J. Klenk, P. H. Whincup, E. E. Dooley, K. Pettee Gabriel, P. Palta, L. A. Pompeii, A. Chernofsky, M. G. Larson, R. S. Vasan, N. Spartano, M. Ballin, P. Nordstrom, A. Nordstrom, S. A. Anderssen, B. H. Hansen, J. A. Cochrane, T. Dwyer, J. Wang, L. Ferrucci, F. Liu, J. Schrack, J. Urbanek, P. F. Saint-Maurice, N. Yamamoto, Y. Yoshitake, R. L. Newton, Jr., S. Yang, E. J. Shiroma, J. E. Fulton, and Collaborative Steps for Health. "Daily Steps and All-Cause Mortality: A Meta-Analysis of 15 International Cohorts." *Lancet Public Health* 7, no. 3 (2022): e219-e28.
6. Halaweh, H., C. Willen, A. Grimby-Ekman, and U. Svantesson. "Physical Activity and Health-Related Quality of Life among Community Dwelling Elderly." *J Clin Med Res* 7, no. 11 (2015): 845-52.
7. Anokye, N. K., P. Trueman, C. Green, T. G. Pavey, and R. S. Taylor. "Physical Activity and Health Related Quality of Life." *BMC Public Health* 12 (2012): 624.
8. Posadzki, P., D. Pieper, R. Bajpai, H. Makaruk, N. Konsgen, A. L. Neuhaus, and M. Semwal. "Exercise/Physical Activity and Health Outcomes: An Overview of Cochrane Systematic Reviews." *BMC Public Health* 20, no. 1 (2020): 1724.
9. Carson, K. V., M. G. Chandratilleke, J. Picot, M. P. Brinn, A. J. Esterman, and B. J. Smith. "Physical Training for Asthma." *Cochrane Database Syst Rev*, no. 9 (2013): CD001116.
10. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization; 2010. APPENDIX 5, GLOSSARY. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305048/.
11. Garber, C. E., B. Blissmer, M. R. Deschenes, B. A. Franklin, M. J. Lamonte, I. M. Lee, D. C. Nieman, D. P. Swain, and Medicine American College of Sports. "American College of Sports Medicine Position Stand. Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults:

Guidance for Prescribing Exercise." *Med Sci Sports Exerc* 43, no. 7 (2011): 1334-59.
12. Jette, M., K. Sidney, and G. Blumchen. "Metabolic Equivalents (Mets) in Exercise Testing, Exercise Prescription, and Evaluation of Functional Capacity." *Clin Cardiol* 13, no. 8 (1990): 555-65.
13. Ainsworth, B. E., W. L. Haskell, S. D. Herrmann, N. Meckes, D. R. Bassett, Jr., C. Tudor-Locke, J. L. Greer, J. Vezina, M. C. Whitt-Glover, and A. S. Leon. "2011 Compendium of Physical Activities: A Second Update of Codes and Met Values." *Med Sci Sports Exerc* 43, no. 8 (2011): 1575-81.
14. Haskell, W. L., I. M. Lee, R. R. Pate, K. E. Powell, S. N. Blair, B. A. Franklin, C. A. Macera, G. W. Heath, P. D. Thompson, A. Bauman, Medicine American College of Sports, and Association American Heart. "Physical Activity and Public Health: Updated Recommendation for Adults from the American College of Sports Medicine and the American Heart Association." *Circulation* 116, no. 9 (2007): 1081-93.
15. Byrne, N. M., A. P. Hills, G. R. Hunter, R. L. Weinsier, and Y. Schutz. "Metabolic Equivalent: One Size Does Not Fit All." *J Appl Physiol (1985)* 99, no. 3 (2005): 1112-9.
16. Hall, K. S., C. A. Howe, S. R. Rana, C. L. Martin, and M. C. Morey. "Mets and Accelerometry of Walking in Older Adults: Standard Versus Measured Energy Cost." *Med Sci Sports Exerc* 45, no. 3 (2013): 574-82.
17. Kokkinos, P., C. Faselis, J. Myers, X. Sui, J. Zhang, and S. N. Blair. "Age-Specific Exercise Capacity Threshold for Mortality Risk Assessment in Male Veterans." *Circulation* 130, no. 8 (2014): 653-8.
18. Mendes, M. A., I. da Silva, V. Ramires, F. Reichert, R. Martins, R. Ferreira, and E. Tomasi. "Metabolic Equivalent of Task (Mets) Thresholds as an Indicator of Physical Activity Intensity." *PLoS One* 13, no. 7 (2018): e0200701.
19. "World Health Organisation, Global Physical Activity Questionnaire (Gpaq) Analysis Guide, Available At: Https://Cdn.Who.Int/Media/Docs/Default-Source/Ncds/Ncd-Surveillance/Gpaq-Analysis-Guide.Pdf?Sfvrsn=1e83d571_2."
20. "U.S. Department of Health and Human Services. Physical Activity Guidelines for Americans, 2nd Edition. Washington, Dc: U.S. Department of Health and Human Services; 2018. Available At: Https://Health.Gov/Our-Work/Nutrition-Physical-Activity/Physical-Activity-Guidelines/Current-Guidelines."
21. "Uk Chief Medical Officers' Physical Activity Guidelines.; 2019. Available At: Https://Www.Gov.Uk/Government/Publications/Physical-Activity-Guidelines-Uk-Chief-Medical-Officers-Report."
22. "Physical Activity and Exercise Guidelines for All Australians; 2021. Available At: Https://Www.Health.Gov.Au/Health-Topics/Physical-Activity-and-Exercise/Physical-Activity-and-Exercise-Guidelines-for-All-Australians#Order-the-Guidelines."
23. Millard, L. A. C., K. Tilling, T. R. Gaunt, D. Carslake, and D. A. Lawlor. "Association of Physical Activity Intensity and Bout Length with Mortality: An Observational Study of 79,503 Uk Biobank Participants." *PLoS Med* 18, no. 9 (2021): e1003757.
24. Choi, Y., and J. W. Choi. "Changes in the Frequency of Moderate-to-Vigorous Physical Activity and Subsequent Risk of All-Cause and Cardiovascular Disease Mortality." *Int J Environ Res Public Health* 19, no. 1 (2022).

25. Kyu, H. H., V. F. Bachman, L. T. Alexander, J. E. Mumford, A. Afshin, K. Estep, J. L. Veerman, K. Delwiche, M. L. Iannarone, M. L. Moyer, K. Cercy, T. Vos, C. J. Murray, and M. H. Forouzanfar. "Physical Activity and Risk of Breast Cancer, Colon Cancer, Diabetes, Ischemic Heart Disease, and Ischemic Stroke Events: Systematic Review and Dose-Response Meta-Analysis for the Global Burden of Disease Study 2013." *BMJ* 354 (2016): i3857.
26. Wang, Y., J. Nie, G. Ferrari, J. P. Rey-Lopez, and L. F. M. Rezende. "Association of Physical Activity Intensity with Mortality: A National Cohort Study of 403681 Us Adults." *JAMA Intern Med* 181, no. 2 (2021): 203-11.
27. "World Health Organization Global Recommendations on Physical Activity for Health. Geneva: World Health Organization, 2010.".
28. Jakicic, J. M., W. E. Kraus, K. E. Powell, W. W. Campbell, K. F. Janz, R. P. Troiano, K. Sprow, A. Torres, K. L. Piercy, and Committee Physical Activity Guidelines Advisory. "Association between Bout Duration of Physical Activity and Health: Systematic Review." *Med Sci Sports Exerc* 51, no. 6 (2019): 1213-19.
29. "Moderate-to-Vigorous Physical Activity and All-Cause Mortality: Do Bouts Matter?". *J Am Heart Assoc* 7, no. 23 (2018): e03713.
30. Tudor-Locke, C., C. L. Craig, Y. Aoyagi, R. C. Bell, K. A. Croteau, I. De Bourdeaudhuij, B. Ewald, A. W. Gardner, Y. Hatano, L. D. Lutes, S. M. Matsudo, F. A. Ramirez-Marrero, L. Q. Rogers, D. A. Rowe, M. D. Schmidt, M. A. Tully, and S. N. Blair. "How Many Steps/Day Are Enough? For Older Adults and Special Populations." *Int J Behav Nutr Phys Act* 8 (2011): 80.
31. Tudor-Locke, C., C. L. Craig, J. P. Thyfault, and J. C. Spence. "A Step-Defined Sedentary Lifestyle Index: <5000 Steps/Day." *Appl Physiol Nutr Metab* 38, no. 2 (2013): 100-14.
32. Lee, I. M., E. J. Shiroma, M. Kamada, D. R. Bassett, C. E. Matthews, and J. E. Buring. "Association of Step Volume and Intensity with All-Cause Mortality in Older Women." *JAMA Intern Med* 179, no. 8 (2019): 1105-12.
33. Tudor-Locke, C., C. L. Craig, W. J. Brown, S. A. Clemes, K. De Cocker, B. Giles-Corti, Y. Hatano, S. Inoue, S. M. Matsudo, N. Mutrie, J. M. Oppert, D. A. Rowe, M. D. Schmidt, G. M. Schofield, J. C. Spence, P. J. Teixeira, M. A. Tully, and S. N. Blair. "How Many Steps/Day Are Enough? For Adults." *Int J Behav Nutr Phys Act* 8 (2011): 79.
34. "Goldstein Re. Exercise Capacity. In: Walker Hk, Hall Wd, Hurst Jw, Editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd Edition. Boston: Butterworths; 1990. Chapter 8. Available From: Https://Www.Ncbi.Nlm.Nih.Gov/Books/Nbk404/. ."
35. Pitta, F., T. Troosters, M. A. Spruit, V. S. Probst, M. Decramer, and R. Gosselink. "Characteristics of Physical Activities in Daily Life in Chronic Obstructive Pulmonary Disease." *Am J Respir Crit Care Med* 171, no. 9 (2005): 972-7.
36. Gommans, L. N., D. Hageman, I. Jansen, R. de Gee, R. C. van Lummel, N. Verhofstad, M. R. Scheltinga, and J. A. Teijink. "Minimal Correlation between Physical Exercise Capacity and Daily Activity in Patients with Intermittent Claudication." *J Vasc Surg* 63, no. 4 (2016): 983-9.
37. Laboratories, A. T. S. Committee on Proficiency Standards for Clinical Pulmonary Function. "Ats Statement: Guidelines for the Six-Minute Walk Test." *Am J Respir Crit Care Med* 166, no. 1 (2002): 111-7.

38. Fastenau, A., O. C. van Schayck, R. Gosselink, K. C. Aretz, and J. W. Muris. "Discrepancy between Functional Exercise Capacity and Daily Physical Activity: A Cross-Sectional Study in Patients with Mild to Moderate Copd." *Prim Care Respir J* 22, no. 4 (2013): 425-30.
39. "Alves Mariana Agnes Da Silva, Bueno Flávia Regina, Haraguchi Lays Ikumi Hirose, Corrêa Fernanda Rocha, Dourado Victor Zuniga. Correlation between Average Number of Steps Per Day and the Six-Minute Walk Test in Asymptomatic Adults and Elderly. Fisioter. Pesqui. [Internet]. 2013 June [Cited 2020 Jan 05] ; 20(2): 123-129. ."
40. Skender, S., J. Ose, J. Chang-Claude, M. Paskow, B. Bruhmann, E. M. Siegel, K. Steindorf, and C. M. Ulrich. "Accelerometry and Physical Activity Questionnaires - a Systematic Review." *BMC Public Health* 16 (2016): 515.
41. Ferrari, P., C. Friedenreich, and C. E. Matthews. "The Role of Measurement Error in Estimating Levels of Physical Activity." *Am J Epidemiol* 166, no. 7 (2007): 832-40.
42. Neilson, H. K., P. J. Robson, C. M. Friedenreich, and I. Csizmadi. "Estimating Activity Energy Expenditure: How Valid Are Physical Activity Questionnaires?" *Am J Clin Nutr* 87, no. 2 (2008): 279-91.
43. Starling, R. D., D. E. Matthews, P. A. Ades, and E. T. Poehlman. "Assessment of Physical Activity in Older Individuals: A Doubly Labeled Water Study." *J Appl Physiol (1985)* 86, no. 6 (1999): 2090-6.
44. Helmerhorst, H. J., S. Brage, J. Warren, H. Besson, and U. Ekelund. "A Systematic Review of Reliability and Objective Criterion-Related Validity of Physical Activity Questionnaires." *Int J Behav Nutr Phys Act* 9 (2012): 103.
45. Migueles, J. H., C. Cadenas-Sanchez, U. Ekelund, C. Delisle Nystrom, J. Mora-Gonzalez, M. Lof, I. Labayen, J. R. Ruiz, and F. B. Ortega. "Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations." *Sports Med* 47, no. 9 (2017): 1821-45.
46. Avallone, K. M., and A. C. McLeish. "Asthma and Aerobic Exercise: A Review of the Empirical Literature." *J Asthma* 50, no. 2 (2013): 109-16.
47. Ford, E. S., G. W. Heath, D. M. Mannino, and S. C. Redd. "Leisure-Time Physical Activity Patterns among Us Adults with Asthma." *Chest* 124, no. 2 (2003): 432-7.
48. Teramoto, M., and S. Moonie. "Physical Activity Participation among Adult Nevadans with Self-Reported Asthma." *J Asthma* 48, no. 5 (2011): 517-22.
49. Malkia, E., and O. Impivaara. "Intensity of Physical Activity and Respiratory Function in Subjects with and without Bronchial Asthma." *Scand J Med Sci Sports* 8, no. 1 (1998): 27-32.
50. Wertz, D. A., M. Pollack, K. Rodgers, R. L. Bohn, P. Sacco, and S. D. Sullivan. "Impact of Asthma Control on Sleep, Attendance at Work, Normal Activities, and Disease Burden." *Ann Allergy Asthma Immunol* 105, no. 2 (2010): 118-23.
51. Cordova-Rivera, L., P. G. Gibson, P. A. Gardiner, and V. M. McDonald. "A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes." *J Allergy Clin Immunol Pract* 6, no. 6 (2018): 1968-81 e2.
52. Scott, H. A., P. G. Gibson, M. L. Garg, J. J. Pretto, P. J. Morgan, R. Callister, and L. G. Wood. "Dietary Restriction and Exercise Improve Airway

Inflammation and Clinical Outcomes in Overweight and Obese Asthma: A Randomized Trial." *Clin Exp Allergy* 43, no. 1 (2013): 36-49.
53. Tudor-Locke, C., Y. Hatano, R. P. Pangrazi, and M. Kang. "Revisiting "How Many Steps Are Enough?"." *Med Sci Sports Exerc* 40, no. 7 Suppl (2008): S537-43.
54. "Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available From: Www.Ginasthma.Org."
55. Chung, K. F., S. E. Wenzel, J. L. Brozek, A. Bush, M. Castro, P. J. Sterk, I. M. Adcock, E. D. Bateman, E. H. Bel, E. R. Bleecker, L. P. Boulet, C. Brightling, P. Chanez, S. E. Dahlen, R. Djukanovic, U. Frey, M. Gaga, P. Gibson, Q. Hamid, N. N. Jajour, T. Mauad, R. L. Sorkness, and W. G. Teague. "International Ers/Ats Guidelines on Definition, Evaluation and Treatment of Severe Asthma." *Eur Respir J* 43, no. 2 (2014): 343-73.
56. Hyland, M. E., B. Whalley, R. C. Jones, and M. Masoli. "A Qualitative Study of the Impact of Severe Asthma and Its Treatment Showing That Treatment Burden Is Neglected in Existing Asthma Assessment Scales." *Qual Life Res* 24, no. 3 (2015): 631-9.
57. Foster, J. M., V. M. McDonald, M. Guo, and H. K. Reddel. ""I Have Lost in Every Facet of My Life": The Hidden Burden of Severe Asthma." *Eur Respir J* 50, no. 3 (2017).
58. Cordova-Rivera, L., P. G. Gibson, P. A. Gardiner, H. Powell, and V. M. McDonald. "Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations." *J Allergy Clin Immunol Pract* 6, no. 3 (2018): 814-22.
59. Neale, J., M. W. Orme, S. Majd, S. Chantrell, S. J. Singh, P. Bradding, R. H. Green, and R. A. Evans. "A Comparison of Daily Physical Activity Profiles between Adults with Severe Asthma and Healthy Controls." *Eur Respir J* 56, no. 1 (2020).
60. Bahmer, T., B. Waschki, F. Schatz, C. Herzmann, P. Zabel, A. M. Kirsten, K. F. Rabe, H. Watz, and E. RA-Study Group. "Physical Activity, Airway Resistance and Small Airway Dysfunction in Severe Asthma." *Eur Respir J* 49, no. 1 (2017).
61. Hennegrave, F., O. Le Rouzic, S. Fry, H. Behal, C. Chenivesse, and B. Wallaert. "Factors Associated with Daily Life Physical Activity in Patients with Asthma." *Health Sci Rep* 1, no. 10 (2018): e84.
62. Cordova-Rivera, L., P. G. Gibson, P. A. Gardiner, and V. M. McDonald. "Physical Activity Associates with Disease Characteristics of Severe Asthma, Bronchiectasis and Copd." *Respirology* 24, no. 4 (2019): 352-60.
63. Clark, C. J., and L. M. Cochrane. "Assessment of Work Performance in Asthma for Determination of Cardiorespiratory Fitness and Training Capacity." *Thorax* 43, no. 10 (1988): 745-9.
64. Freeman, W., G. E. Packe, and R. M. Cayton. "Effect of Nebulised Salbutamol on Maximal Exercise Performance in Men with Mild Asthma." *Thorax* 44, no. 11 (1989): 942-7.
65. Rossman, M. J., S. Nader, D. Berry, F. Orsini, A. Klansky, and H. C. Haverkamp. "Effects of Altered Airway Function on Exercise Ventilation in Asthmatic Adults." *Med Sci Sports Exerc* 46, no. 6 (2014): 1104-13.
66. van 't Hul, A. J., S. Frouws, E. van den Akker, R. van Lummel, A. Starrenburg-Razenberg, A. van Bruggen, G. J. Braunstahl, and J. C. In 't Veen. "Decreased Physical Activity in Adults with Bronchial Asthma." *Respir Med* 114 (2016): 72-7.

67. Verlaet, A., A. Moreira, A. Sa-Sousa, R. Barros, R. Santos, P. Moreira, and J. Fonseca. "Physical Activity in Adults with Controlled and Uncontrolled Asthma as Compared to Healthy Adults: A Cross-Sectional Study." *Clin Transl Allergy* 3, no. 1 (2013): 1.
68. Ritz, T., D. Rosenfield, and A. Steptoe. "Physical Activity, Lung Function, and Shortness of Breath in the Daily Life of Individuals with Asthma." *Chest* 138, no. 4 (2010): 913-8.
69. Russell, M. A., C. Janson, F. G. Real, A. Johannessen, M. Waatevik, B. Benediktsdottir, M. Holm, E. Lindberg, V. Schlunssen, W. Raza, S. C. Dharmage, and C. Svanes. "Physical Activity and Asthma: A Longitudinal and Multi-Country Study." *J Asthma* 54, no. 9 (2017): 938-45.
70. Bonini, M., and P. Palange. "Exercise-Induced Bronchoconstriction: New Evidence in Pathogenesis, Diagnosis and Treatment." *Asthma Res Pract* 1 (2015): 2.
71. Pavord, I. D., N. Mathieson, A. Scowcroft, R. Pedersini, G. Isherwood, and D. Price. "The Impact of Poor Asthma Control among Asthma Patients Treated with Inhaled Corticosteroids Plus Long-Acting Beta2-Agonists in the United Kingdom: A Cross-Sectional Analysis." *NPJ Prim Care Respir Med* 27, no. 1 (2017): 17.
72. Haselkorn, T., H. Chen, D. P. Miller, J. E. Fish, S. P. Peters, S. T. Weiss, and C. A. Jones. "Asthma Control and Activity Limitations: Insights from the Real-World Evaluation of Asthma Control and Treatment (React) Study." *Ann Allergy Asthma Immunol* 104, no. 6 (2010): 471-7.
73. Abdo, M., B. Waschki, A. M. Kirsten, F. Trinkmann, H. Biller, C. Herzmann, E. von Mutius, M. Kopp, G. Hansen, K. F. Rabe, T. Bahmer, H. Watz, and Alliance study group. "Persistent Uncontrolled Asthma: Long-Term Impact on Physical Activity and Body Composition." *J Asthma Allergy* 14 (2021): 229-40.
74. Bruno, A., C. G. Uasuf, G. Insalaco, R. Barazzoni, A. Ballacchino, M. Gjomarkaj, and E. Pace. "Nutritional Status and Physical Inactivity in Moderated Asthmatics: A Pilot Study." *Medicine (Baltimore)* 95, no. 31 (2016): e4485.
75. Boulet, L. P. "Asthma and Obesity." *Clin Exp Allergy* 43, no. 1 (2013): 8-21.
76. Battaglia, S., A. Benfante, M. Spatafora, and N. Scichilone. "Asthma in the Elderly: A Different Disease?" *Breathe (Sheff)* 12, no. 1 (2016): 18-28.
77. Zein, J. G., R. A. Dweik, S. A. Comhair, E. R. Bleecker, W. C. Moore, S. P. Peters, W. W. Busse, N. N. Jarjour, W. J. Calhoun, M. Castro, K. F. Chung, A. Fitzpatrick, E. Israel, W. G. Teague, S. E. Wenzel, T. E. Love, B. M. Gaston, S. C. Erzurum, and Program Severe Asthma Research. "Asthma Is More Severe in Older Adults." *PLoS One* 10, no. 7 (2015): e0133490.
78. Fuseini, H., and D. C. Newcomb. "Mechanisms Driving Gender Differences in Asthma." *Curr Allergy Asthma Rep* 17, no. 3 (2017): 19.
79. Chowdhury, N. U., V. P. Guntur, D. C. Newcomb, and M. E. Wechsler. "Sex and Gender in Asthma." *Eur Respir Rev* 30, no. 162 (2021).
80. Hsu, J., J. Chen, and M. C. Mirabelli. "Asthma Morbidity, Comorbidities, and Modifiable Factors among Older Adults." *J Allergy Clin Immunol Pract* 6, no. 1 (2018): 236-43 e7.
81. Adams, R. J., D. H. Wilson, A. W. Taylor, A. Daly, E. Tursan d'Espaignet, E. Dal Grande, and R. E. Ruffin. "Psychological Factors and Asthma Quality of Life: A Population Based Study." *Thorax* 59, no. 11 (2004): 930-5.

82. Hull, J. H., E. S. Walsted, M. J. Pavitt, A. Menzies-Gow, V. Backer, and G. Sandhu. "High Prevalence of Laryngeal Obstruction During Exercise in Severe Asthma." *Am J Respir Crit Care Med* 199, no. 4 (2019): 538-42.
83. Ritz, T., A. E. Meuret, A. F. Trueba, A. Fritzsche, and A. von Leupoldt. "Psychosocial Factors and Behavioral Medicine Interventions in Asthma." *J Consult Clin Psychol* 81, no. 2 (2013): 231-50.
84. Ritz, T., A. Kullowatz, C. Bobb, B. Dahme, H. Magnussen, F. Kanniess, and A. Steptoe. "Psychological Triggers and Hyperventilation Symptoms in Asthma." *Ann Allergy Asthma Immunol* 100, no. 5 (2008): 426-32.
85. Agache, I., C. Ciobanu, G. Paul, and L. Rogozea. "Dysfunctional Breathing Phenotype in Adults with Asthma - Incidence and Risk Factors." *Clin Transl Allergy* 2, no. 1 (2012): 18.
86. Low, K., L. Ruane, N. Uddin, P. Finlay, K. K. Lau, K. Hamza, P. W. Holmes, G. Hamilton, and P. G. Bardin. "Abnormal Vocal Cord Movement in Patients with and without Airway Obstruction and Asthma Symptoms." *Clin Exp Allergy* 47, no. 2 (2017): 200-07.
87. Tiotiu, A., I. Ioan, N. Wirth, R. Romero-Fernandez, and F. J. Gonzalez-Barcala. "The Impact of Tobacco Smoking on Adult Asthma Outcomes." *Int J Environ Res Public Health* 18, no. 3 (2021).
88. Strine, T. W., L. S. Balluz, and E. S. Ford. "The Associations between Smoking, Physical Inactivity, Obesity, and Asthma Severity in the General Us Population." *J Asthma* 44, no. 8 (2007): 651-8.
89. Nyenhuis, S. M., A. E. Dixon, and J. Ma. "Impact of Lifestyle Interventions Targeting Healthy Diet, Physical Activity, and Weight Loss on Asthma in Adults: What Is the Evidence?" *J Allergy Clin Immunol Pract* 6, no. 3 (2018): 751-63.
90. Shim, Y. M., A. Burnette, S. Lucas, R. C. Herring, J. Weltman, J. T. Patrie, A. L. Weltman, and T. A. Platts-Mills. "Physical Deconditioning as a Cause of Breathlessness among Obese Adolescents with a Diagnosis of Asthma." *PLoS One* 8, no. 4 (2013): e61022.
91. Faleiro, R. C., E. V. Mancuzo, F. C. Lanza, Mvnp Queiroz, L. F. L. de Oliveira, V. O. Ganem, and L. B. Lasmar. "Exercise Limitation in Children and Adolescents with Severe Refractory Asthma: A Lack of Asthma Control?" *Front Physiol* 11 (2020): 620736.
92. Deng, X., J. Ma, Y. Yuan, Z. Zhang, and W. Niu. "Association between Overweight or Obesity and the Risk for Childhood Asthma and Wheeze: An Updated Meta-Analysis on 18 Articles and 73 252 Children." *Pediatr Obes* 14, no. 9 (2019): e12532.
93. Beckett, W. S., D. R. Jacobs, Jr., X. Yu, C. Iribarren, and O. D. Williams. "Asthma Is Associated with Weight Gain in Females but Not Males, Independent of Physical Activity." *Am J Respir Crit Care Med* 164, no. 11 (2001): 2045-50.
94. Jerning, C., E. Martinander, A. Bjerg, L. Ekerljung, K. A. Franklin, B. Jarvholm, K. Larsson, A. Malinovschi, R. Middelveld, M. Emtner, and C. Janson. "Asthma and Physical Activity--a Population Based Study Results from the Swedish Ga(2)Len Survey." *Respir Med* 107, no. 11 (2013): 1651-8.
95. Tashiro, Hiroki, and Stephanie A. Shore. "Obesity and Severe Asthma." *Allergology International* 68, no. 2 (2019): 135-42.
96. Denlinger, L. C., B. R. Phillips, S. Ramratnam, K. Ross, N. R. Bhakta, J. C. Cardet, M. Castro, S. P. Peters, W. Phipatanakul, S. Aujla, L. B. Bacharier, E.

R. Bleecker, S. A. Comhair, A. Coverstone, M. DeBoer, S. C. Erzurum, S. B. Fain, M. Fajt, A. M. Fitzpatrick, J. Gaffin, B. Gaston, A. T. Hastie, G. A. Hawkins, F. Holguin, A. M. Irani, E. Israel, B. D. Levy, N. Ly, D. A. Meyers, W. C. Moore, R. Myers, M. T. Opina, M. C. Peters, M. L. Schiebler, R. L. Sorkness, W. G. Teague, S. E. Wenzel, P. G. Woodruff, D. T. Mauger, J. V. Fahy, N. N. Jarjour, Lung National Heart, and Investigators Blood Institute's Severe Asthma Research Program. "Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations." *Am J Respir Crit Care Med* 195, no. 3 (2017): 302-13.

97. Fitzpatrick, S., R. Joks, and J. I. Silverberg. "Obesity Is Associated with Increased Asthma Severity and Exacerbations, and Increased Serum Immunoglobulin E in Inner-City Adults." *Clin Exp Allergy* 42, no. 5 (2012): 747-59.
98. Freitas, P. D., A. G. Silva, P. G. Ferreira, D. A. Silva A, J. M. Salge, R. M. Carvalho-Pinto, A. Cukier, C. M. Brito, M. C. Mancini, and C. R. F. Carvalho. "Exercise Improves Physical Activity and Comorbidities in Obese Adults with Asthma." *Med Sci Sports Exerc* 50, no. 7 (2018): 1367-76.
99. Sutherland, E. R., E. Goleva, M. Strand, D. A. Beuther, and D. Y. Leung. "Body Mass and Glucocorticoid Response in Asthma." *Am J Respir Crit Care Med* 178, no. 7 (2008): 682-7.
100. Peters, M. C., K. W. McGrath, G. A. Hawkins, A. T. Hastie, B. D. Levy, E. Israel, B. R. Phillips, D. T. Mauger, S. A. Comhair, S. C. Erzurum, M. W. Johansson, N. N. Jarjour, A. M. Coverstone, M. Castro, F. Holguin, S. E. Wenzel, P. G. Woodruff, E. R. Bleecker, J. V. Fahy, Lung National Heart, and Program Blood Institute Severe Asthma Research. "Plasma Interleukin-6 Concentrations, Metabolic Dysfunction, and Asthma Severity: A Cross-Sectional Analysis of Two Cohorts." *Lancet Respir Med* 4, no. 7 (2016): 574-84.
101. Teng, Y. K., J. L. Huang, K. W. Yeh, L. S. Fu, C. H. Lin, W. F. Ma, S. D. Lee, and L. C. Chiang. "Influential Factors of Insufficient Physical Activity among Adolescents with Asthma in Taiwan." *PLoS One* 9, no. 12 (2014): e116417.
102. Peters, U., A. E. Dixon, and E. Forno. "Obesity and Asthma." *J Allergy Clin Immunol* 141, no. 4 (2018): 1169-79.
103. Dogra, S., J. Baker, and C. I. Ardern. "The Role of Physical Activity and Body Mass Index in the Health Care Use of Adults with Asthma." *Ann Allergy Asthma Immunol* 102, no. 6 (2009): 462-8.
104. Shi, S., H. Huang, R. Zheng, N. Zhang, W. Dai, J. Liang, and Y. Dai. "Can Long-Term Regular Physical Activity Improve Health Outcomes among Adults with Asthma-Evidence from a Systematic Review and Bayesian Meta-Analysis." *Ann Transl Med* 10, no. 6 (2022): 338.
105. Eijkemans, M., M. Mommers, J. M. Draaisma, C. Thijs, and M. H. Prins. "Physical Activity and Asthma: A Systematic Review and Meta-Analysis." *PLoS One* 7, no. 12 (2012): e50775.
106. Brumpton, B. M., A. Langhammer, M. A. Ferreira, Y. Chen, and X. M. Mai. "Physical Activity and Incident Asthma in Adults: The Hunt Study, Norway." *BMJ Open* 6, no. 11 (2016): e013856.
107. Russell, M. A., S. Dharmage, E. Fuertes, A. Marcon, A. E. Carsin, S. Pascual Erquicia, J. Heinrich, A. Johannessen, M. J. Abramson, A. F. S. Amaral, I. Cerveri, P. Demoly, V. Garcia-Larsen, D. Jarvis, J. Martinez-Moratalla, D. Nowak, L. Palacios-Gomez, G. Squillacioti, W. Raza, M. Emtner, and J.

Garcia-Aymerich. "The Effect of Physical Activity on Asthma Incidence over 10 Years: Population-Based Study." *ERJ Open Res* 7, no. 1 (2021).
108. Driessen, L. M., J. C. Kiefte-de Jong, V. W. Jaddoe, A. Hofman, H. Raat, J. C. de Jongste, and H. A. Moll. "Physical Activity and Respiratory Symptoms in Children: The Generation R Study." *Pediatr Pulmonol* 49, no. 1 (2014): 36-42.
109. Garcia-Aymerich, J., R. Varraso, J. M. Anto, and C. A. Camargo, Jr. "Prospective Study of Physical Activity and Risk of Asthma Exacerbations in Older Women." *Am J Respir Crit Care Med* 179, no. 11 (2009): 999-1003.
110. Doggett, N., and S. Dogra. "Physical Inactivity and Television-Viewing Time among Aboriginal Adults with Asthma: A Cross-Sectional Analysis of the Aboriginal Peoples Survey." *Health Promot Chronic Dis Prev Can* 35, no. 3 (2015): 54-61.
111. Ford, E. S., D. M. Mannino, S. C. Redd, D. G. Moriarty, and A. H. Mokdad. "Determinants of Quality of Life among People with Asthma: Findings from the Behavioral Risk Factor Surveillance System." *J Asthma* 41, no. 3 (2004): 327-36.
112. Lucas, S. R., and T. A. Platts-Mills. "Physical Activity and Exercise in Asthma: Relevance to Etiology and Treatment." *J Allergy Clin Immunol* 115, no. 5 (2005): 928-34.
113. Workman, A. D., R. M. Carey, B. Chen, C. J. Saunders, P. Marambaud, C. H. Mitchell, M. G. Tordoff, R. J. Lee, and N. A. Cohen. "Calhm1-Mediated Atp Release and Ciliary Beat Frequency Modulation in Nasal Epithelial Cells." *Sci Rep* 7, no. 1 (2017): 6687.
114. Brumpton, B. M., A. Langhammer, A. H. Henriksen, C. A. Camargo, Jr., Y. Chen, P. R. Romundstad, and X. M. Mai. "Physical Activity and Lung Function Decline in Adults with Asthma: The Hunt Study." *Respirology* 22, no. 2 (2017): 278-83.
115. Loponen, J., P. Ilmarinen, L. E. Tuomisto, O. Niemela, M. Tommola, P. Nieminen, L. Lehtimaki, and H. Kankaanranta. "Daily Physical Activity and Lung Function Decline in Adult-Onset Asthma: A 12-Year Follow-up Study." *Eur Clin Respir J* 5, no. 1 (2018): 1533753.
116. Petersen, A. M., and B. K. Pedersen. "The Anti-Inflammatory Effect of Exercise." *J Appl Physiol (1985)* 98, no. 4 (2005): 1154-62.
117. Gleeson, M., N. C. Bishop, D. J. Stensel, M. R. Lindley, S. S. Mastana, and M. A. Nimmo. "The Anti-Inflammatory Effects of Exercise: Mechanisms and Implications for the Prevention and Treatment of Disease." *Nat Rev Immunol* 11, no. 9 (2011): 607-15.
118. Ford, E. S. "Does Exercise Reduce Inflammation? Physical Activity and C-Reactive Protein among U.S. Adults." *Epidemiology* 13, no. 5 (2002): 561-8.
119. Franca-Pinto, A., F. A. Mendes, R. M. de Carvalho-Pinto, R. C. Agondi, A. Cukier, R. Stelmach, B. M. Saraiva-Romanholo, J. Kalil, M. A. Martins, P. Giavina-Bianchi, and C. R. Carvalho. "Aerobic Training Decreases Bronchial Hyperresponsiveness and Systemic Inflammation in Patients with Moderate or Severe Asthma: A Randomised Controlled Trial." *Thorax* 70, no. 8 (2015): 732-9.
120. Silva, R. A., F. M. Almeida, C. R. Olivo, B. M. Saraiva-Romanholo, M. A. Martins, and C. R. Carvalho. "Exercise Reverses Ova-Induced Inhibition of Glucocorticoid Receptor and Increases Anti-Inflammatory Cytokines in Asthma." *Scand J Med Sci Sports* 26, no. 1 (2016): 82-92.

121. Handzlik, M. K., A. J. Shaw, M. Dungey, N. C. Bishop, and M. Gleeson. "The Influence of Exercise Training Status on Antigen-Stimulated Il-10 Production in Whole Blood Culture and Numbers of Circulating Regulatory T Cells." *Eur J Appl Physiol* 113, no. 7 (2013): 1839-48.
122. Olivo, C. R., R. P. Vieira, F. M. Arantes-Costa, A. Perini, M. A. Martins, and C. R. Carvalho. "Effects of Aerobic Exercise on Chronic Allergic Airway Inflammation and Remodeling in Guinea Pigs." *Respir Physiol Neurobiol* 182, no. 2-3 (2012): 81-7.
123. Pastva, A., K. Estell, T. R. Schoeb, T. P. Atkinson, and L. M. Schwiebert. "Aerobic Exercise Attenuates Airway Inflammatory Responses in a Mouse Model of Atopic Asthma." *J Immunol* 172, no. 7 (2004): 4520-6.
124. Vieira, R. P., R. C. Claudino, A. C. Duarte, A. B. Santos, A. Perini, H. C. Faria Neto, T. Mauad, M. A. Martins, M. Dolhnikoff, and C. R. Carvalho. "Aerobic Exercise Decreases Chronic Allergic Lung Inflammation and Airway Remodeling in Mice." *Am J Respir Crit Care Med* 176, no. 9 (2007): 871-7.
125. Mackenzie, B., A. S. Andrade-Sousa, M. C. Oliveira-Junior, E. Assumpcao-Neto, M. A. Brandao-Rangel, A. Silva-Renno, A. Santos-Dias, S. Cicko, M. Grimm, T. Muller, A. P. Oliveira, M. A. Martins, M. Idzko, and R. P. Vieira. "Dendritic Cells Are Involved in the Effects of Exercise in a Model of Asthma." *Med Sci Sports Exerc* 48, no. 8 (2016): 1459-67.
126. de Araujo, C. C., P. S. Marques, J. D. Silva, C. S. Samary, A. L. da Silva, I. Henriques, M. A. Antunes, M. V. de Oliveira, R. C. Goldenberg, M. M. Morales, I. Abreu, B. L. Diaz, N. N. Rocha, V. L. Capelozzi, and P. R. Rocco. "Regular and Moderate Aerobic Training before Allergic Asthma Induction Reduces Lung Inflammation and Remodeling." *Scand J Med Sci Sports* 26, no. 11 (2016): 1360-72.
127. Zarneshan, A., and M. Gholamnejad. "Moderate Aerobic Exercise Enhances the Th1/Th2 Ratio in Women with Asthma." *Tanaffos* 18, no. 3 (2019): 230-37.
128. Silva, R. A., R. P. Vieira, A. C. Duarte, F. D. Lopes, A. Perini, T. Mauad, M. A. Martins, and C. R. Carvalho. "Aerobic Training Reverses Airway Inflammation and Remodelling in an Asthma Murine Model." *Eur Respir J* 35, no. 5 (2010): 994-1002.
129. Mendes, F. A., F. M. Almeida, A. Cukier, R. Stelmach, W. Jacob-Filho, M. A. Martins, and C. R. Carvalho. "Effects of Aerobic Training on Airway Inflammation in Asthmatic Patients." *Med Sci Sports Exerc* 43, no. 2 (2011): 197-203.
130. Prossegger, J., D. Huber, C. Grafetstatter, C. Pichler, H. Braunschmid, R. Weisbock-Erdheim, and A. Hartl. "Winter Exercise Reduces Allergic Airway Inflammation: A Randomized Controlled Study." *Int J Environ Res Public Health* 16, no. 11 (2019).
131. Scott, H. A., J. R. Latham, R. Callister, J. J. Pretto, K. Baines, N. Saltos, J. W. Upham, and L. G. Wood. "Acute Exercise Is Associated with Reduced Exhaled Nitric Oxide in Physically Inactive Adults with Asthma." *Ann Allergy Asthma Immunol* 114, no. 6 (2015): 470-9.
132. Pakhale, S., V. Luks, A. Burkett, and L. Turner. "Effect of Physical Training on Airway Inflammation in Bronchial Asthma: A Systematic Review." *BMC Pulm Med* 13 (2013): 38.
133. Turi, K. N., L. Romick-Rosendale, K. K. Ryckman, and T. V. Hartert. "A Review of Metabolomics Approaches and Their Application in Identifying Causal

Pathways of Childhood Asthma." *J Allergy Clin Immunol* 141, no. 4 (2018): 1191-201.
134. Kelly, R. S., A. Dahlin, M. J. McGeachie, W. Qiu, J. Sordillo, E. S. Wan, A. C. Wu, and J. Lasky-Su. "Asthma Metabolomics and the Potential for Integrative Omics in Research and the Clinic." *Chest* 151, no. 2 (2017): 262-77.
135. Kelly, R. S., M. P. Kelly, and P. Kelly. "Metabolomics, Physical Activity, Exercise and Health: A Review of the Current Evidence." *Biochim Biophys Acta Mol Basis Dis* 1866, no. 12 (2020): 165936.
136. Estaki, M., J. Pither, P. Baumeister, J. P. Little, S. K. Gill, S. Ghosh, Z. Ahmadi-Vand, K. R. Marsden, and D. L. Gibson. "Cardiorespiratory Fitness as a Predictor of Intestinal Microbial Diversity and Distinct Metagenomic Functions." *Microbiome* 4, no. 1 (2016): 42.
137. Welly, R. J., T. W. Liu, T. M. Zidon, J. L. Rowles, 3rd, Y. M. Park, T. N. Smith, K. S. Swanson, J. Padilla, and V. J. Vieira-Potter. "Comparison of Diet Versus Exercise on Metabolic Function and Gut Microbiota in Obese Rats." *Med Sci Sports Exerc* 48, no. 9 (2016): 1688-98.
138. Denou, E., K. Marcinko, M. G. Surette, G. R. Steinberg, and J. D. Schertzer. "High-Intensity Exercise Training Increases the Diversity and Metabolic Capacity of the Mouse Distal Gut Microbiota During Diet-Induced Obesity." *Am J Physiol Endocrinol Metab* 310, no. 11 (2016): E982-93.
139. Campbell, S. C., P. J. Wisniewski, M. Noji, L. R. McGuinness, M. M. Haggblom, S. A. Lightfoot, L. B. Joseph, and L. J. Kerkhof. "The Effect of Diet and Exercise on Intestinal Integrity and Microbial Diversity in Mice." *PLoS One* 11, no. 3 (2016): e0150502.
140. Turner, S., P. Eastwood, A. Cook, and S. Jenkins. "Improvements in Symptoms and Quality of Life Following Exercise Training in Older Adults with Moderate/Severe Persistent Asthma." *Respiration* 81, no. 4 (2011): 302-10.
141. Jaakkola, J. J. K., S. A. M. Aalto, S. Hernberg, S. P. Kiihamaki, and M. S. Jaakkola. "Regular Exercise Improves Asthma Control in Adults: A Randomized Controlled Trial." *Sci Rep* 9, no. 1 (2019): 12088.
142. Mendes, F. A., R. C. Goncalves, M. P. Nunes, B. M. Saraiva-Romanholo, A. Cukier, R. Stelmach, W. Jacob-Filho, M. A. Martins, and C. R. Carvalho. "Effects of Aerobic Training on Psychosocial Morbidity and Symptoms in Patients with Asthma: A Randomized Clinical Trial." *Chest* 138, no. 2 (2010): 331-7.
143. Emtner, M., M. Finne, and G. Stalenheim. "A 3-Year Follow-up of Asthmatic Patients Participating in a 10-Week Rehabilitation Program with Emphasis on Physical Training." *Arch Phys Med Rehabil* 79, no. 5 (1998): 539-44.
144. Boyd, A., C. T. Yang, K. Estell, C. T. Ms, L. B. Gerald, M. Dransfield, M. Bamman, J. Bonner, T. P. Atkinson, and L. M. Schwiebert. "Feasibility of Exercising Adults with Asthma: A Randomized Pilot Study." *Allergy Asthma Clin Immunol* 8, no. 1 (2012): 13.
145. Saxer, S., S. R. Schneider, P. Appenzeller, P. R. Bader, M. Lichtblau, M. Furian, U. Sheraliev, B. Estebesova, B. Emilov, T. Sooronbaev, K. E. Bloch, and S. Ulrich. "Asthma Rehabilitation at High Vs. Low Altitude: Randomized Parallel-Group Trial." *BMC Pulm Med* 19, no. 1 (2019): 134.
146. Freitas, P. D., P. G. Ferreira, A. G. Silva, R. Stelmach, R. M. Carvalho-Pinto, F. L. Fernandes, M. C. Mancini, M. N. Sato, M. A. Martins, and C. R. Carvalho.

"The Role of Exercise in a Weight-Loss Program on Clinical Control in Obese Adults with Asthma. A Randomized Controlled Trial." *Am J Respir Crit Care Med* 195, no. 1 (2017): 32-42.
147. Toennesen, L. L., H. Meteran, M. Hostrup, N. R. Wium Geiker, C. B. Jensen, C. Porsbjerg, A. Astrup, J. Bangsbo, D. Parker, and V. Backer. "Effects of Exercise and Diet in Nonobese Asthma Patients-a Randomized Controlled Trial." *J Allergy Clin Immunol Pract* 6, no. 3 (2018): 803-11.
148. Turk, Y., W. Theel, A. van Huisstede, G. M. van de Geijn, E. Birnie, P. S. Hiemstra, J. K. Sont, C. Taube, and G. J. Braunstahl. "Short-Term and Long-Term Effect of a High-Intensity Pulmonary Rehabilitation Programme in Obese Patients with Asthma: A Randomised Controlled Trial." *Eur Respir J* 56, no. 1 (2020).
149. Kuder, M. M., M. Clark, C. Cooley, V. Prieto-Centurion, A. Danley, I. Riley, A. Siddiqi, K. Weller, S. Kitsiou, and S. M. Nyenhuis. "A Systematic Review of the Effect of Physical Activity on Asthma Outcomes." *J Allergy Clin Immunol Pract* 9, no. 9 (2021): 3407-21 e8.
150. McLoughlin, R. F., V. L. Clark, P. D. Urroz, P. G. Gibson, and V. M. McDonald. "Increasing Physical Activity in Severe Asthma: A Systematic Review and Meta-Analysis." *Eur Respir J* (2022).
151. Eichenberger, P. A., S. N. Diener, R. Kofmehl, and C. M. Spengler. "Effects of Exercise Training on Airway Hyperreactivity in Asthma: A Systematic Review and Meta-Analysis." *Sports Med* 43, no. 11 (2013): 1157-70.
152. Meyer, A., S. Gunther, T. Volmer, K. Taube, and H. J. Baumann. "A 12-Month, Moderate-Intensity Exercise Training Program Improves Fitness and Quality of Life in Adults with Asthma: A Controlled Trial." *BMC Pulm Med* 15 (2015): 56.
153. Hewitt, M., K. Estell, I. C. Davis, and L. M. Schwiebert. "Repeated Bouts of Moderate-Intensity Aerobic Exercise Reduce Airway Reactivity in a Murine Asthma Model." *Am J Respir Cell Mol Biol* 42, no. 2 (2010): 243-9.
154. Geiger, K. R., and N. Henschke. "Swimming for Children and Adolescents with Asthma." *Br J Sports Med* 49, no. 12 (2015): 835-6.
155. Grande, A. J., V. Silva, B. N. Andriolo, R. Riera, S. A. Parra, and M. S. Peccin. "Water-Based Exercise for Adults with Asthma." *Cochrane Database Syst Rev*, no. 7 (2014): CD010456.
156. Arandelovic, M., I. Stankovic, and M. Nikolic. "Swimming and Persons with Mild Persistant Asthma." *ScientificWorldJournal* 7 (2007): 1182-8.
157. Rijssenbeek-Nouwens, L. H., K. B. Fieten, A. O. Bron, S. Hashimoto, E. H. Bel, and E. J. Weersink. "High-Altitude Treatment in Atopic and Nonatopic Patients with Severe Asthma." *Eur Respir J* 40, no. 6 (2012): 1374-80.
158. Grootendorst, D. C., S. E. Dahlen, J. W. Van Den Bos, E. J. Duiverman, M. Veselic-Charvat, E. J. Vrijlandt, S. O'Sullivan, M. Kumlin, P. J. Sterk, and A. C. Roldaan. "Benefits of High Altitude Allergen Avoidance in Atopic Adolescents with Moderate to Severe Asthma, over and above Treatment with High Dose Inhaled Steroids." *Clin Exp Allergy* 31, no. 3 (2001): 400-8.
159. Boulet, L. P., and P. M. O'Byrne. "Asthma and Exercise-Induced Bronchoconstriction in Athletes." *N Engl J Med* 372, no. 7 (2015): 641-8.
160. Arie, S. "What Can We Learn from Asthma in Elite Athletes?" *BMJ* 344 (2012): e2556.
161. Couto, M., J. Stang, L. Horta, T. Stensrud, M. Severo, P. Mowinckel, D. Silva, L. Delgado, A. Moreira, and K. H. Carlsen. "Two Distinct Phenotypes of

Asthma in Elite Athletes Identified by Latent Class Analysis." *J Asthma* 52, no. 9 (2015): 897-904.
162. Burns, J., C. Mason, N. Mueller, J. Ohlander, J. P. Zock, F. Drobnic, B. Wolfarth, J. Heinrich, E. Omenaas, T. Stensrud, D. Nowak, K. Radon, G. A2LEN-Olympic Study-Team, and Survey European Community Respiratory Health. "Asthma Prevalence in Olympic Summer Athletes and the General Population: An Analysis of Three European Countries." *Respir Med* 109, no. 7 (2015): 813-20.
163. Gawlik, R., M. Kurowski, M. Kowalski, Z. Zietkowski, A. Pokrywka, H. Krysztofiak, J. Krzywanski, A. Bugajski, and Z. Bartuzi. "Asthma and Exercise-Induced Respiratory Disorders in Athletes. The Position Paper of the Polish Society of Allergology and Polish Society of Sports Medicine." *Postepy Dermatol Alergol* 36, no. 1 (2019): 1-10.
164. Bentzon, A. K., L. W. Loehde, V. Backer, and L. Toennesen. "The Long-Term Effect of an Exercise and Diet Intervention in Asthma Patients: A 1-Year Follow-up on a Randomised Controlled Trial." *ERJ Open Res* 5, no. 2 (2019).
165. Wood, L. G., M. L. Garg, J. M. Smart, H. A. Scott, D. Barker, and P. G. Gibson. "Manipulating Antioxidant Intake in Asthma: A Randomized Controlled Trial." *Am J Clin Nutr* 96, no. 3 (2012): 534-43.
166. Wood, L. G., N. Shivappa, B. S. Berthon, P. G. Gibson, and J. R. Hebert. "Dietary Inflammatory Index Is Related to Asthma Risk, Lung Function and Systemic Inflammation in Asthma." *Clin Exp Allergy* 45, no. 1 (2015): 177-83.
167. Coelho, C. M., M. M. Reboredo, F. M. Valle, C. Malaguti, L. A. Campos, L. M. Nascimento, E. V. Carvalho, J. C. A. Oliveira, and B. V. Pinheiro. "Effects of an Unsupervised Pedometer-Based Physical Activity Program on Daily Steps of Adults with Moderate to Severe Asthma: A Randomized Controlled Trial." *J Sports Sci* 36, no. 10 (2018): 1186-93.
168. Evaristo, K. B., F. A. R. Mendes, M. G. Saccomani, A. Cukier, R. M. Carvalho-Pinto, M. R. Rodrigues, D. F. Santaella, B. M. Saraiva-Romanholo, M. A. Martins, and C. R. F. Carvalho. "Effects of Aerobic Training Versus Breathing Exercises on Asthma Control: A Randomized Trial." *J Allergy Clin Immunol Pract* 8, no. 9 (2020): 2989-96 e4.
169. Spruit, M. A., S. J. Singh, C. Garvey, R. Zuwallack, L. Nici, C. Rochester, K. Hill, A. E. Holland, S. C. Lareau, W. D. Man, F. Pitta, L. Sewell, J. Raskin, J. Bourbeau, R. Crouch, F. M. Franssen, R. Casaburi, J. H. Vercoulen, I. Vogiatzis, R. Gosselink, E. M. Clini, T. W. Effing, F. Maltais, J. van der Palen, T. Troosters, D. J. Janssen, E. Collins, J. Garcia-Aymerich, D. Brooks, B. F. Fahy, M. A. Puhan, M. Hoogendoorn, R. Garrod, A. M. Schols, B. Carlin, R. Benzo, P. Meek, M. Morgan, M. P. Rutten-van Molken, A. L. Ries, B. Make, R. S. Goldstein, C. A. Dowson, J. L. Brozek, C. F. Donner, E. F. Wouters, and Ats Ers Task Force on Pulmonary Rehabilitation. "An Official American Thoracic Society/European Respiratory Society Statement: Key Concepts and Advances in Pulmonary Rehabilitation." *Am J Respir Crit Care Med* 188, no. 8 (2013): e13-64.
170. Rochester, C. L., I. Vogiatzis, A. E. Holland, S. C. Lareau, D. D. Marciniuk, M. A. Puhan, M. A. Spruit, S. Masefield, R. Casaburi, E. M. Clini, R. Crouch, J. Garcia-Aymerich, C. Garvey, R. S. Goldstein, K. Hill, M. Morgan, L. Nici, F. Pitta, A. L. Ries, S. J. Singh, T. Troosters, P. J. Wijkstra, B. P. Yawn, R. L. ZuWallack, and Ats Ers Task Force on Policy in Pulmonary Rehabilitation. "An Official American Thoracic Society/European Respiratory Society Policy

Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation." *Am J Respir Crit Care Med* 192, no. 11 (2015): 1373-86.
171. Spruit, M. A., F. Pitta, E. McAuley, R. L. ZuWallack, and L. Nici. "Pulmonary Rehabilitation and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease." *Am J Respir Crit Care Med* 192, no. 8 (2015): 924-33.
172. Carpagnano, G. E., F. Sessa, G. Scioscia, D. Lacedonia, M. P. Foschino, M. P. Venuti, A. I. Triggiani, A. Valenzano, O. Resta, G. Cibelli, and G. Messina. "Physical Activity as a New Tool to Evaluate the Response to Omalizumab and Mepolizumab in Severe Asthmatic Patients: A Pilot Study." *Front Pharmacol* 10 (2019): 1630.
173. King, A. C., S. N. Blair, D. E. Bild, R. K. Dishman, P. M. Dubbert, B. H. Marcus, N. B. Oldridge, R. S. Paffenbarger, Jr., K. E. Powell, and K. K. Yeager. "Determinants of Physical Activity and Interventions in Adults." *Med Sci Sports Exerc* 24, no. 6 Suppl (1992): S221-36.
174. Freitas, P. D., R. F. Xavier, N. F. P. Passos, R. M. Carvalho-Pinto, A. Cukier, M. A. Martins, V. Cavalheri, K. Hill, R. Stelmach, and C. R. F. Carvalho. "Effects of a Behaviour Change Intervention Aimed at Increasing Physical Activity on Clinical Control of Adults with Asthma: Study Protocol for a Randomised Controlled Trial." *BMC Sports Sci Med Rehabil* 11 (2019): 16.
175. Scichilone, N., A. Benfante, M. Bocchino, F. Braido, P. Paggiaro, A. Papi, P. Santus, and A. Sanduzzi. "Which Factors Affect the Choice of the Inhaler in Chronic Obstructive Respiratory Diseases?" *Pulm Pharmacol Ther* 31 (2015): 63-7.
176. Mancuso, C. A., T. N. Choi, H. Westermann, S. Wenderoth, J. P. Hollenberg, M. T. Wells, A. M. Isen, J. B. Jobe, J. P. Allegrante, and M. E. Charlson. "Increasing Physical Activity in Patients with Asthma through Positive Affect and Self-Affirmation: A Randomized Trial." *Arch Intern Med* 172, no. 4 (2012): 337-43.
177. Freitas, P. D., N. F. P. Passos, R. M. Carvalho-Pinto, M. A. Martins, V. Cavalheri, K. Hill, R. Stelmach, and C. R. F. Carvalho. "A Behavior Change Intervention Aimed at Increasing Physical Activity Improves Clinical Control in Adults with Asthma: A Randomized Controlled Trial." *Chest* 159, no. 1 (2021): 46-57.
178. Panagiotou, M., N. G. Koulouris, and N. Rovina. "Physical Activity: A Missing Link in Asthma Care." *J Clin Med* 9, no. 3 (2020).
179. "The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network, 2018.".
180. Asher, M. I., L. Garcia-Marcos, N. E. Pearce, and D. P. Strachan. "Trends in Worldwide Asthma Prevalence." *Eur Respir J* 56, no. 6 (2020).
181. Santus, P., M. Saad, G. Damiani, V. Patella, and D. Radovanovic. "Current and Future Targeted Therapies for Severe Asthma: Managing Treatment with Biologics Based on Phenotypes and Biomarkers." *Pharmacol Res* 146 (2019): 104296.
182. Chupp, G. L., E. S. Bradford, F. C. Albers, D. J. Bratton, J. Wang-Jairaj, L. M. Nelsen, J. L. Trevor, A. Magnan, and A. Ten Brinke. "Efficacy of Mepolizumab Add-on Therapy on Health-Related Quality of Life and Markers of Asthma Control in Severe Eosinophilic Asthma (Musca): A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group, Multicentre, Phase 3b Trial." *Lancet Respir Med* 5, no. 5 (2017): 390-400.

183. Bermejo, I., M. Stevenson, K. Cooper, S. Harnan, J. Hamilton, M. Clowes, C. Carroll, T. Harrison, and S. Saha. "Mepolizumab for Treating Severe Eosinophilic Asthma: An Evidence Review Group Perspective of a Nice Single Technology Appraisal." *Pharmacoeconomics* 36, no. 2 (2018): 131-44.
184. Holguin, F., J. C. Cardet, K. F. Chung, S. Diver, D. S. Ferreira, A. Fitzpatrick, M. Gaga, L. Kellermeyer, S. Khurana, S. Knight, V. M. McDonald, R. L. Morgan, V. E. Ortega, D. Rigau, P. Subbarao, T. Tonia, I. M. Adcock, E. R. Bleecker, C. Brightling, L. P. Boulet, M. Cabana, M. Castro, P. Chanez, A. Custovic, R. Djukanovic, U. Frey, B. Frankemolle, P. Gibson, D. Hamerlijnck, N. Jarjour, S. Konno, H. Shen, C. Vitary, and A. Bush. "Management of Severe Asthma: A European Respiratory Society/American Thoracic Society Guideline." *Eur Respir J* 55, no. 1 (2020).
185. Sin, D. D., M. Miravitlles, D. M. Mannino, J. B. Soriano, D. Price, B. R. Celli, J. M. Leung, Y. Nakano, H. Y. Park, P. A. Wark, and M. E. Wechsler. "What Is Asthma-Copd Overlap Syndrome? Towards a Consensus Definition from a Round Table Discussion." *Eur Respir J* 48, no. 3 (2016): 664-73.
186. Nathan, R. A., C. A. Sorkness, M. Kosinski, M. Schatz, J. T. Li, P. Marcus, J. J. Murray, and T. B. Pendergraft. "Development of the Asthma Control Test: A Survey for Assessing Asthma Control." *J Allergy Clin Immunol* 113, no. 1 (2004): 59-65.
187. Schatz, M., M. Kosinski, A. S. Yarlas, J. Hanlon, M. E. Watson, and P. Jhingran. "The Minimally Important Difference of the Asthma Control Test." *J Allergy Clin Immunol* 124, no. 4 (2009): 719-23 e1.
188. Jones, P. W., F. H. Quirk, and C. M. Baveystock. "The St George's Respiratory Questionnaire." *Respir Med* 85 Suppl B (1991): 25-31; discussion 33-7.
189. Jones, P. W. "Interpreting Thresholds for a Clinically Significant Change in Health Status in Asthma and Copd." *Eur Respir J* 19, no. 3 (2002): 398-404.
190. Gelpi, M., J. Argentiero, P. W. Jones, and A. Ronit. "A Scoring Application for the St. George's Respiratory Questionnaire." *Chest* 150, no. 3 (2016): 747-8.
191. Albers, F. C., D. J. Bratton, N. B. Gunsoy, S. M. Cockle, R. Alfonso-Cristancho, and G. J. Braunstahl. "Mepolizumab Improves Work Productivity, Activity Limitation, Symptoms, and Rescue Medication Use in Severe Eosinophilic Asthma." *Clin Respir J* 16, no. 3 (2022): 252-58.
192. Dijkstra, B., Y. Kamsma, and W. Zijlstra. "Detection of Gait and Postures Using a Miniaturised Triaxial Accelerometer-Based System: Accuracy in Community-Dwelling Older Adults." *Age Ageing* 39, no. 2 (2010): 259-62.
193. van Hees, V. T., R. C. van Lummel, and K. R. Westerterp. "Estimating Activity-Related Energy Expenditure under Sedentary Conditions Using a Tri-Axial Seismic Accelerometer." *Obesity (Silver Spring)* 17, no. 6 (2009): 1287-92.
194. de Groot, S., and M. G. Nieuwenhuizen. "Validity and Reliability of Measuring Activities, Movement Intensity and Energy Expenditure with the Dynaport Movemonitor." *Med Eng Phys* 35, no. 10 (2013): 1499-505.
195. Storm, F. A., B. W. Heller, and C. Mazza. "Step Detection and Activity Recognition Accuracy of Seven Physical Activity Monitors." *PLoS One* 10, no. 3 (2015): e0118723.
196. Rabinovich, R. A., Z. Louvaris, Y. Raste, D. Langer, H. Van Remoortel, S. Giavedoni, C. Burtin, E. M. Regueiro, I. Vogiatzis, N. S. Hopkinson, M. I. Polkey, F. J. Wilson, W. Macnee, K. R. Westerterp, T. Troosters, and P. ROactive Consortium. "Validity of Physical Activity Monitors During Daily Life in Patients with Copd." *Eur Respir J* 42, no. 5 (2013): 1205-15.

197. Van Remoortel, H., Y. Raste, Z. Louvaris, S. Giavedoni, C. Burtin, D. Langer, F. Wilson, R. Rabinovich, I. Vogiatzis, N. S. Hopkinson, T. Troosters, and P. ROactive consortium. "Validity of Six Activity Monitors in Chronic Obstructive Pulmonary Disease: A Comparison with Indirect Calorimetry." *PLoS One* 7, no. 6 (2012): e39198.
198. van Schooten, K. S., J. H. van Dieen, M. Pijnappels, A. B. Maier, A. J. van 't Hul, M. Niessen, and R. C. van Lummel. "The Association between Age and Accelerometry-Derived Types of Habitual Daily Activity: An Observational Study over the Adult Life Span in the Netherlands." *BMC Public Health* 18, no. 1 (2018): 824.
199. van Schooten, K. S., S. M. Rispens, P. J. Elders, P. Lips, J. H. van Dieen, and M. Pijnappels. "Assessing Physical Activity in Older Adults: Required Days of Trunk Accelerometer Measurements for Reliable Estimation." *J Aging Phys Act* 23, no. 1 (2015): 9-17.
200. Bassett, D. R., Jr., L. P. Toth, S. R. LaMunion, and S. E. Crouter. "Step Counting: A Review of Measurement Considerations and Health-Related Applications." *Sports Med* 47, no. 7 (2017): 1303-15.
201. Rist, C., N. Karlsson, S. Necander, and C. A. Da Silva. "Physical Activity End-Points in Trials of Chronic Respiratory Diseases: Summary of Evidence." *ERJ Open Res* 8, no. 1 (2022).
202. Louvaris, Z., E. A. Kortianou, S. Spetsioti, M. Vasilopoulou, I. Nasis, A. Asimakos, S. Zakynthinos, and I. Vogiatzis. "Intensity of Daily Physical Activity Is Associated with Central Hemodynamic and Leg Muscle Oxygen Availability in Copd." *J Appl Physiol (1985)* 115, no. 6 (2013): 794-802.
203. Kortianou, E. A., A. Aliverti, Z. Louvaris, M. Vasilopoulou, I. Nasis, A. Asimakos, S. Zakynthinos, and I. Vogiatzis. "Limitation in Tidal Volume Expansion Partially Determines the Intensity of Physical Activity in Copd." *J Appl Physiol (1985)* 118, no. 1 (2015): 107-14.
204. Vorrink, S. N., H. S. Kort, T. Troosters, and J. W. Lammers. "Level of Daily Physical Activity in Individuals with Copd Compared with Healthy Controls." *Respir Res* 12 (2011): 33.
205. Koreny, M., H. Demeyer, M. Benet, A. Arbillaga-Etxarri, E. Balcells, A. Barberan-Garcia, E. Gimeno-Santos, N. S. Hopkinson, C. De Jong, N. Karlsson, Z. Louvaris, M. I. Polkey, M. A. Puhan, R. A. Rabinovich, R. Rodriguez-Roisin, P. Vall-Casas, I. Vogiatzis, T. Troosters, J. Garcia-Aymerich, Group Urban Training Study, P. ROactive Consortium members, Group Urban Training Study, and P. ROactive Consortium members. "Patterns of Physical Activity Progression in Patients with Copd." *Arch Bronconeumol (Engl Ed)* 57, no. 3 (2021): 214-23.
206. Burge, A. T., N. S. Cox, M. J. Abramson, and A. E. Holland. "Interventions for Promoting Physical Activity in People with Chronic Obstructive Pulmonary Disease (Copd)." *Cochrane Database Syst Rev* 4 (2020): CD012626.
207. Hardtstock, F., J. Krieger, T. Wilke, M. Lukas, B. Ultsch, R. Welte, R. Quinzler, U. Maywald, and H. Timmermann. "Use of Biologic Therapies in the Treatment of Asthma - a Comparative Real World Data Analysis on Healthcare Resource Utilization and Costs before and after Therapy Initiation." *J Asthma Allergy* 15 (2022): 407-18.
208. Ortega, H. G., M. C. Liu, I. D. Pavord, G. G. Brusselle, J. M. FitzGerald, A. Chetta, M. Humbert, L. E. Katz, O. N. Keene, S. W. Yancey, P. Chanez, and

Mensa Investigators. "Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma." *N Engl J Med* 371, no. 13 (2014): 1198-207.
209. Bel, E. H., S. E. Wenzel, P. J. Thompson, C. M. Prazma, O. N. Keene, S. W. Yancey, H. G. Ortega, I. D. Pavord, and Sirius Investigators. "Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma." *N Engl J Med* 371, no. 13 (2014): 1189-97.
210. Khurana, S., G. G. Brusselle, E. H. Bel, J. M. FitzGerald, M. Masoli, S. Korn, M. Kato, F. C. Albers, E. S. Bradford, M. J. Gilson, R. G. Price, and M. Humbert. "Long-Term Safety and Clinical Benefit of Mepolizumab in Patients with the Most Severe Eosinophilic Asthma: The Cosmex Study." *Clin Ther* 41, no. 10 (2019): 2041-56 e5.
211. Howarth, P., G. Chupp, L. M. Nelsen, E. S. Bradford, D. J. Bratton, S. G. Smith, F. C. Albers, G. Brusselle, and C. Bachert. "Severe Eosinophilic Asthma with Nasal Polyposis: A Phenotype for Improved Sinonasal and Asthma Outcomes with Mepolizumab Therapy." *J Allergy Clin Immunol* 145, no. 6 (2020): 1713-15.
212. Santanello, N. C., J. Zhang, B. Seidenberg, T. F. Reiss, and B. L. Barber. "What Are Minimal Important Changes for Asthma Measures in a Clinical Trial?" *Eur Respir J* 14, no. 1 (1999): 23-7.
213. Lemiere, C., C. Taille, J. K. Lee, S. G. Smith, S. Mallett, F. C. Albers, E. S. Bradford, S. W. Yancey, and M. C. Liu. "Impact of Baseline Clinical Asthma Characteristics on the Response to Mepolizumab: A Post Hoc Meta-Analysis of Two Phase Iii Trials." *Respir Res* 22, no. 1 (2021): 184.
214. Graff, S., G. Brusselle, S. Hanon, C. Sohy, L. Dupont, R. Peche, A. Michils, C. Pilette, G. Joos, L. Lahousse, T. Lapperre, R. Louis, and F. Schleich. "Anti-Interleukin-5 Therapy Is Associated with Attenuated Lung Function Decline in Severe Eosinophilic Asthma Patients from the Belgian Severe Asthma Registry." *J Allergy Clin Immunol Pract* 10, no. 2 (2022): 467-77.
215. Maglio, A., C. Vitale, S. Pellegrino, C. Calabrese, M. D'Amato, A. Molino, C. Pelaia, M. Triggiani, G. Pelaia, C. Stellato, and A. Vatrella. "Real-Life Effectiveness of Mepolizumab on Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity in Patients with Severe Eosinophilic Asthma." *Biomedicines* 9, no. 11 (2021).
216. "Https://Nucalahcp.Com/Severe-Eosinophilic-Asthma/Dosing-and-Administration/in-Office-Dosing/."
217. Khatri, S., W. Moore, P. G. Gibson, R. Leigh, A. Bourdin, J. Maspero, M. Barros, R. Buhl, P. Howarth, F. C. Albers, E. S. Bradford, M. Gilson, R. G. Price, S. W. Yancey, and H. Ortega. "Assessment of the Long-Term Safety of Mepolizumab and Durability of Clinical Response in Patients with Severe Eosinophilic Asthma." *J Allergy Clin Immunol* 143, no. 5 (2019): 1742-51 e7.
218. "Https://Nucalahcp.Com/Severe-Eosinophilic-Asthma/Safety/."
219. Harrison, T., G. W. Canonica, G. Chupp, J. Lee, F. Schleich, T. Welte, A. Valero, K. Gemzoe, A. Maxwell, S. Joksaite, S. Yang, P. Howarth, and M. K. Van Dyke. "Real-World Mepolizumab in the Prospective Severe Asthma Realiti-a Study: Initial Analysis." *Eur Respir J* 56, no. 4 (2020).
220. Nixon, R., R. Despiney, and P. Pfeffer. "Case of Paradoxical Adverse Response to Mepolizumab with Mepolizumab-Induced Alopecia in Severe Eosinophilic Asthma." *BMJ Case Rep* 13, no. 2 (2020).
221. Mukherjee, M., H. F. Lim, S. Thomas, D. Miller, M. Kjarsgaard, B. Tan, R. Sehmi, N. Khalidi, and P. Nair. "Airway Autoimmune Responses in Severe

Eosinophilic Asthma Following Low-Dose Mepolizumab Therapy." *Allergy Asthma Clin Immunol* 13 (2017): 2.
222. Sokic, M. K., M. Rijavec, P. Korosec, U. Bidovec-Stojkovic, I. Kern, R. Vantur, and S. Skrgat. "Heterogeneous Response of Airway Eosinophilia to Anti-Il-5 Biologics in Severe Asthma Patients." *J Pers Med* 12, no. 1 (2022).
223. Sheng, M., J. Yang, M. Bao, T. Chen, R. Cai, N. Zhang, H. Chen, M. Liu, X. Wu, B. Zhang, Y. Liu, and J. Chao. "The Relationships between Step Count and All-Cause Mortality and Cardiovascular Events: A Dose-Response Meta-Analysis." *J Sport Health Sci* 10, no. 6 (2021): 620-28.
224. Demeyer, H., C. Burtin, M. Hornikx, C. A. Camillo, H. Van Remoortel, D. Langer, W. Janssens, and T. Troosters. "The Minimal Important Difference in Physical Activity in Patients with Copd." *PLoS One* 11, no. 4 (2016): e0154587.
225. Stockwell, S., M. Trott, M. Tully, J. Shin, Y. Barnett, L. Butler, D. McDermott, F. Schuch, and L. Smith. "Changes in Physical Activity and Sedentary Behaviours from before to During the Covid-19 Pandemic Lockdown: A Systematic Review." *BMJ Open Sport Exerc Med* 7, no. 1 (2021): e000960.
226. Puccinelli, P. J., T. S. da Costa, A. Seffrin, C. A. B. de Lira, R. L. Vancini, P. T. Nikolaidis, B. Knechtle, T. Rosemann, L. Hill, and M. S. Andrade. "Correction To: Reduced Level of Physical Activity During Covid-19 Pandemic Is Associated with Depression and Anxiety Levels: An Internet-Based Survey." *BMC Public Health* 21, no. 1 (2021): 613.