



Physical activity and asthma: A longitudinal and multi-country study

Melissa A. Russell, Christer Janson, Francisco Gómez Real, Ane Johannessen, Marie Waatevik, Bryndis Benediktsdóttir, Mathias Holm, Eva Lindberg, Vivi Schlünssen, Wasif Raza, Shyamali C. Dharmage & Cecilie Svanes

To cite this article: Melissa A. Russell, Christer Janson, Francisco Gómez Real, Ane Johannessen, Marie Waatevik, Bryndis Benediktsdóttir, Mathias Holm, Eva Lindberg, Vivi Schlünssen, Wasif Raza, Shyamali C. Dharmage & Cecilie Svanes (2017): Physical activity and asthma: A longitudinal and multi-country study, Journal of Asthma, DOI: [10.1080/02770903.2017.1281293](https://doi.org/10.1080/02770903.2017.1281293)

To link to this article: <http://dx.doi.org/10.1080/02770903.2017.1281293>



View supplementary material [↗](#)



Accepted author version posted online: 16 Feb 2017.
Published online: 16 Feb 2017.



Submit your article to this journal [↗](#)



Article views: 15



View related articles [↗](#)



View Crossmark data [↗](#)

Physical activity and asthma: A longitudinal and multi-country study

Melissa A. Russell^{a,b}, Christer Janson^c, Francisco Gómez Real^{d,e}, Ane Johannessen^f, Marie Waatevik^g, Bryndis Benediktsdóttir^{h,i}, Mathias Holm^j, Eva Lindberg^c, Vivi Schlünssen^{k,l}, Wasif Raza^m, Shyamali C. Dharmage^{a,b}, and Cecilie Svanes^{o,f,n}

^aAllergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, Australia; ^bGastro & Food Allergy Group, Murdoch Children's Research Institute, Melbourne, Australia; ^cDepartment of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden; ^dDepartment of Clinical Science, University of Bergen, Bergen, Norway; ^eDepartment of Gynaecology and Obstetrics, Haukeland University Hospital, Bergen, Norway; ^fCenter for International Health, University of Bergen, Bergen, Norway; ^gCenter for Clinical Research, Haukeland University Hospital, Bergen, Norway; ^hFaculty of Medicine, University of Iceland, Reykjavik, Iceland; ⁱDepartment of Respiratory Medicine and Sleep, The National University Hospital of Iceland, Reykjavik, Iceland; ^jDepartment of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden; ^kDepartment of Public Health, Aarhus University, Aarhus, Denmark; ^lThe National Research Centre for the Working Environment, Copenhagen, Denmark; ^mDivision of Occupational and Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; ⁿDepartment of Occupational Medicine, Haukeland University Hospital, Bergen, Norway

ABSTRACT

Objective: To investigate the impact of physical activity on asthma in middle-aged adults, in one longitudinal analysis, and one multi-centre cross-sectional analysis. **Methods:** The Respiratory Health in Northern Europe (RHINE) is a population-based postal questionnaire cohort study. Physical activity, height and weight were self-reported in Bergen, Norway, at RHINE II (1999–2001) and all centres at RHINE III (2010–2012). A longitudinal analysis of Bergen data investigated the association of baseline physical activity with follow-up asthma, incident asthma and symptoms, using logistic and zero-inflated Poisson regression ($n = 1782$). A cross-sectional analysis of all RHINE III centres investigated the association of physical activity with concurrent asthma and symptoms ($n = 13,542$) using mixed-effects models. Body mass index (BMI) was categorised (<20 , 20 – 24.99 , 25 – 29.99 , $30+$ kg/m²) and physical activity grouped by amount and frequency of lighter (no sweating/heavy breathing) and vigorous (sweating/heavy breathing) activity. **Results:** In the Bergen longitudinal analysis, undertaking light activity 3+ times/week at baseline was associated with less follow-up asthma (odds ratio [OR] 0.44, 95% confidence interval [CI] 0.22, 0.89), whilst an effect from undertaking vigorous activity 3+ times/week was not detected (OR 1.22, 95% CI 0.44, 2.76). The associations were attenuated with BMI adjustment. In the all-centre cross-sectional analysis an interaction was found, with the association between physical activity and asthma varying across BMI categories. **Conclusion:** These findings suggest potential longer-term benefit from lighter physical activity, whilst improvement in asthma outcomes from increasing activity intensity was not evident. Additionally, it appears the benefit from physical activity may differ according to BMI.

ARTICLE HISTORY

Received 17 July 2016
Revised 21 December 2016
Accepted 8 January 2017

KEYWORDS

Adult; asthma; physical exercise; RHINE

Introduction

There is growing interest in the role of physical activity in the aetiology and prognosis of asthma. Physical activity is an attractive option in the management of asthma as it is modifiable, has complimentary health benefits [1], and has shown to be beneficial for other chronic respiratory conditions [2,3].

Systematic reviews of randomised controlled trials (RCTs) have indicated improvement in cardiopulmonary fitness and quality of life from exercise interventions [4,5]; however the longer-term effects on asthma are less

well established. Longitudinal studies show mixed results; some studies suggesting that physical activity is associated with improved asthma outcomes [6–9], while other studies have found no such associations [10,11]. Most of the observational research is cross-sectional [12], with the methodological challenges of reverse causality (i.e. does physical activity precede asthma or vice versa). The role of obesity as a confounder or mediator adds to the complexity. Larger population studies are required to determine the effect of physical activity over time on asthma incidence and prognosis, and also explore the role of obesity.

CONTACT Melissa A. Russell ✉ melissar@unimelb.edu.au Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Level 3, 207 Bouverie Street, Melbourne, Victoria 3010, Australia.

SD and CS are equal contributing authors.

 Supplementary materials for the article can be accessed on the publisher's website at www.tandfonline.com/ijjas.

© 2017 Taylor & Francis Group, LLC

The population-based Respiratory Health in Northern Europe (RHINE) study provided an opportunity to investigate the impact of physical activity on multiple asthma outcomes in middle-aged adults, whilst taking into account body mass index (BMI). The objective of this study was to investigate the effect of physical activity on asthma incidence, prevalence and symptoms, in separate longitudinal and cross-sectional analyses. We hypothesised increased physical activity would be associated with (1) lower asthma incidence, less asthma prevalence and symptoms over ten years; and (2) less concurrent asthma and asthma symptoms consistently across geographical borders.

Material and methods

Study population

RHINE is a population-based cohort from seven Northern European centres that includes a randomly selected sample of men and women, born in 1945–73, from Reykjavik, Iceland; Bergen, Norway; Umeå, Uppsala and Göteborg, Sweden; Aarhus, Denmark; and Tartu, Estonia. In 1991–1993 21,659 persons responded to a postal screening survey as part of the European Community Respiratory Health Survey I/RHINE I, and this cohort was resurveyed in 1999–2001 (RHINE II; 16,106 participants/75%), and 2010–12 (RHINE III, 11,441 participants/53%) [13]. The questions included in the postal survey were translated and back-translated into local languages at each of the centres and the co-ordinating centre then checked all back-translations.

Local ethics committees approved the study and all participants consented to participate.

Participants were excluded from analyses if they reported a doctor diagnosis of Chronic Obstructive Pulmonary Disease (COPD).

RHINE II–RHINE III bergen longitudinal study

Physical activity was recorded only in Bergen in RHINE II and for the purposes of this analysis compared to the asthma outcomes at RHINE III. The Bergen cohort included 3449 participants in RHINE I, with 2506 participants (73%), and 1833 participants (53%) in subsequent follow-ups [13].

RHINE III all centre cross-sectional study

Physical activity was recorded in all centres in RHINE III and for the purposes of this analysis compared cross-sectionally to asthma outcomes across all centres.

Physical activity

In RHINE II Bergen, physical activity was recorded in two questions regarding (1) frequency of lighter activity (no sweating/no heavy breathing), and (2) frequency of vigorous activity (sweating/heavy breathing); response alternatives 0, <1, 1–2 or 3+ times per week. For each question, the lowest two response alternatives were collapsed and defined as ‘no physical activity’ as it was reasoned that there was little material difference between the two categories. The type of physical activity undertaken and length of physical activity sessions were not recorded. Hence, we defined two physical activity variables, ‘frequency of lighter physical activity’ and ‘frequency of vigorous physical activity’, each with three levels (0, 1–2 or 3+ times per week).

In RHINE III physical activity was collected across three questions regarding: (1) frequency, (2) intensity and (3) length of physical activity sessions. These questions have been found to be reliable and correlated with VO2 max [14], and have been used previously in RHINE publications [15] and in many investigations from the Nord-Trøndelag Health (HUNT) study [16–18]. A categorical variable was created by ranking combinations of these questions and then dividing according to the median time spent physically active (1 hour) and whether the activity was light or vigorous (see online supplement). This resulted in five categories of the variable ‘physical activity per week’: no physical activity, ≤1 hour light, >1 hour light, ≤1 hour vigorous and >1 hour vigorous. It should be noted that it was not possible to produce a physical activity variable with the same categories across RHINE II and RHINE III.

Asthma outcomes

Current asthma

Participants reporting at least two of the following three issues were classified as having current asthma: ‘an attack of asthma in the last 12 months’, ‘taking any medicine (including inhalers, aerosols or tablets) for asthma in the past 12 months’ and/or ‘whistling or wheezing in the chest at any time during the last 12 months when you have not had a cold’ [19].

Asthma symptoms

An asthma symptoms count variable, scored 0–8, was formed from answers to eight questions regarding wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks in the last 12 months, and current asthma medication [20]. For each ‘yes’ a score of one was given.

Incident asthma

Incident asthma was obtained from the answers to the RHINE III questions “Do you have or have you ever had asthma?” and “How old were you when you first experienced asthma symptoms?” If participants responded that they had ever asthma in RHINE III but not RHINE II and their reported age of first asthma symptoms was also in this period they were categorized as having incident asthma. This group was compared to the control group of those reporting never asthma in RHINE III. To exclude those who had a history of asthma, participants who reported ‘ever asthma’ in RHINE II or onset of symptoms prior to RHINE II were excluded.

Confounders

Confounders considered were gender, age (continuous), smoking, education (primary, secondary or university/college), previous asthma status and BMI. Smoking was grouped into eight categories (see online supplement). BMI was based on self-reported height and weight and categorised (<20, 20–24.99, 25–29.99 and 30+ kg/m²) to take into account any non-linear associations.

Analysis

RHINE II–RHINE III bergen longitudinal study

Three longitudinal analyses were undertaken in the RHINE II–RHINE III Bergen cohort between baseline (RHINE II) ‘frequency of lighter physical activity’ and ‘frequency of vigorous activity’ and the follow-up (RHINE III) asthma outcome variables (‘current asthma’, ‘asthma symptoms’ and ‘incident asthma’). The two physical activity variables were entered into the analyses concurrently, so the effect of each could be observed whilst adjusting for the other. Gender, age, education, RHINE II smoking and the related baseline asthma variable (i.e. RHINE II current asthma when RHINE III current asthma was the outcome) were identified as confounders using directed acyclic graphs (DAGs) and added to the models. Baseline (RHINE II) categorical BMI was added separately to each model to observe BMI as being on the causal pathway/a potential confounder.

Logistic regression was used with ‘current asthma’ and ‘incident asthma’ outcomes. Zero-inflated Poisson regression was used for the analysis with the outcome ‘asthma symptoms’, a count variable with excess zeroes [21]. Interactions between each physical activity variable and gender, age, RHINE II asthma baseline variables and RHINE II BMI were considered.

The Bergen longitudinal study had 30% power, at a 5% significance level, to detect a reduction in the odds

of current asthma of 0.88 [12] for those undertaking any level of physical activity compared to the base category. Sensitivity analyses were undertaken to investigate (1) reverse causation (analyses adjusting for RHINE I BMI and asthma) (2) and predictors of loss to follow-up (see online supplement for further details).

RHINE III all centre cross-sectional study

Two cross-sectional analyses were undertaken between RHINE III ‘physical activity per week’ and RHINE III ‘current asthma’, and ‘asthma symptoms’. The confounders of gender, age, education, RHINE III smoking and the related baseline asthma variable were identified in a DAG and adjusted for. RHINE III BMI was added separately to each model to observe BMI as being on the causal pathway/a potential confounder. Multilevel mixed-effects models for binary outcomes, with two levels and a random intercept were used with ‘current asthma’ as the outcome, to take into account centre clustering. Zero-inflated Poisson regression, with standard errors allowing for clustering, was used with asthma symptoms as the outcome. Interactions between physical activity per week and gender, age, RHINE II asthma baseline variables and RHINE III BMI were considered. When significant interactions were identified, the effect of physical activity was stratified across the modifying term and presented graphically.

We also undertook a random-effects meta-analysis to investigate heterogeneity in effects across centres. STATA 13 (StataCorp, College Station, TX, USA) was used.

Results

Participant characteristics

In RHINE II–RHINE III Bergen longitudinal study 1,782 participants were available for analyses after excluding 29 participants with COPD. With exclusion of those with asthma at baseline, incident asthma was analysed in 1,573 participants. Participant characteristics are available in Supplementary Table 1.

In the RHINE III all-centre cross-sectional analysis, 13,542 participants were available for analyses, after excluding 358 participants with COPD. Seven per cent of participants had current asthma (Table 1) and the median number of asthma symptoms was 0 (Interquartile Range [IQR] 0–1). Age and sex were evenly distributed across centres, and current asthma was most prevalent in Umeå and Uppsala (Table 1).

Physical activity

In the RHINE II–RHINE III Bergen longitudinal study, 406 (17.3%), 697 (29.7%) and 1246 (53.0%) participants

Table 1. Characteristics of participants in the RHINE III study across centres. Data are presented as *n* (%) unless otherwise specified.

Centre	Aarhus (<i>n</i> = 2268)	Reykjavik (<i>n</i> = 2161)	Bergen (<i>n</i> = 2314)	Goteberg (<i>n</i> = 1690)	Umeå (<i>n</i> = 1922)	Uppsala (<i>n</i> = 1911)	Tartu (<i>n</i> = 1276)	Total ^a (13,542)
Mean age [95% CI]	50 [50, 50]	53 [53, 54]	51 [51, 51]	53 [52, 53]	53 [53, 53]	53 [52, 53]	49 [48, 49]	52 [52, 52]
Female	1,197 (53)	941 (53)	1,160 (50)	899 (53)	1,008 (53)	994 (52)	741 (58)	6,940 (53)
Never smoked	1,016 (45)	678 (40)	892 (39)	796 (48)	1,073 (57)	1,085 (58)	440 (47)	5,980 (48)
Current asthma	92 (4.1)	121 (6.3)	141 (6.1)	94 (5.6)	119 (6.3)	113 (5.9)	44 (3.5)	724 (5.5)
Incident asthma ^b	41 (2.3)	62 (4.6)	55 (3.4)	21 (1.6)	35 (2.3)	35 (3.7)	16 (3.7)	265 (2.8)
Mean BMI kg/m ² (95%CI)	25 [25, 25]	27 [27, 27]	26 [26, 26]	26 [26, 26]	26 [26, 26]	26 [26, 26]	27 [26, 27]	26 [25, 26]
Physical activity per week								
None	498 (23)	559 (34)	411 (18)	403 (25)	321 (17)	405 (22)	267 (23)	2,864 (23)
Lighter, ≤1 hour	301 (14)	164 (9.3)	269 (12)	242 (15)	307 (16)	261 (14)	251 (21)	1,785 (14)
Lighter, >1 hour	219 (9.9)	73 (4.4)	177 (7.8)	134 (8.2)	212 (11)	184 (9.9)	138 (12)	1,137 (9.0)
Vigorous, ≤1 hour	775 (35)	543 (33)	802 (35)	575 (35)	609 (33)	696 (38)	269 (23)	4,269 (34)
Vigorous, >1 hour	415 (19)	334 (20)	614 (27)	287 (18)	420 (23)	309 (17)	234 (20)	2,613 (21)

Notes. CI: confidence interval; BMI: body mass index.

^aNumber of participants with missing data: 1082 for age, 411 for gender, 939 for smoking history, 664 for BMI, 484 for education, 498 for current asthma, 875 for asthma symptoms, 532 for wheeze, 874 for physical activity per week.

^bParticipants excluded because a history of asthma was recorded in RHINE II and/or age of onset of asthma symptoms was prior to RHINE II.

reported no, 1–2 and 3+ sessions of lighter physical activity per week, respectively, and 1134 (50.1%), 787 (34.8%) and 341 (15.1%) participants reported no, 1–2 and 3+ sessions of vigorous physical activity per week, respectively, at baseline.

In the RHINE III all-centre cross-sectional study, 2,864 (23.0%) participants reported no physical activity per week and most frequently participants reported less than an hour of vigorous activity per week (4,269 participants, 34%) (Table 1).

RHINE II–RHINE III bergen longitudinal study

There was a statistically significant linear trend for a protective effect from increasing frequency of lighter physical activity in regard to current asthma, after adjustment for a priori defined confounders ($p_{\text{trend}} = 0.021$) (Table 2). This association was attenuated after BMI adjustment ($p_{\text{trend}} = 0.051$). There was no significant association between vigorous activity at baseline and current asthma at follow-up. There was a modest non-significant trend towards increased odds of current asthma with undertaking vigorous activity 3+ times/week after adjustment for BMI (odds ratio [OR]: 1.51, 95% confidence interval [CI] 0.66, 3.44).

There was no association between the frequency of lighter or vigorous physical activity at baseline and number of asthma symptoms at follow-up or incident asthma (Table 2).

In the sensitivity analysis, there was no material difference with the RHINE I current asthma and RHINE I BMI added into the analyses. Some RHINE II factors were associated with loss to follow-up; however, there was no interaction between the physical activity variables and RHINE II asthma factors in predicting loss to follow-up (Supplement 1).

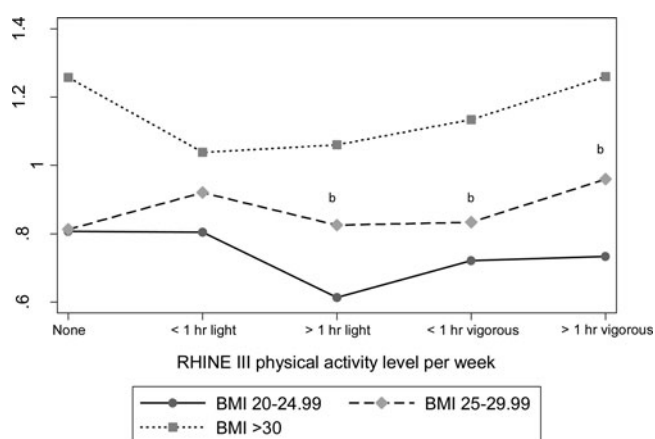


Figure 1. RHINE III all-centre cross-sectional study: interaction between physical activity and BMI categories^a with the outcome of asthma symptoms. (a) BMI <20 not included in the graph due to low numbers of participants in this group. (b) $p < 0.05$ between those with a BMI of 20–24.99 compared to those with a BMI of 25–29.99 at the given levels of physical activity.

RHINE III all-centre cross-sectional study

Physical activity per week and current asthma were not significantly associated in the RHINE III all-centre cross-sectional study before ($p = 0.100$) and after ($p = 0.157$) adjustment for BMI (Table 3).

There was a significant decrease in the number of asthma symptoms when undertaking less than one hour of vigorous physical activity (RR 0.90 95% CI 0.84, 0.96, $p = 0.002$) compared to no physical activity, after adjustment for a priori defined confounders (Table 3). There was an interaction between physical activity and BMI with asthma symptoms as the outcome (Figure 1). It demonstrated that there was a significant decrease in asthma symptoms for participants with a RHINE III BMI of 20–24.99 who undertook light physical activity for an hour or more per week ($p = 0.045$), vigorous physical activity less than an hour ($p = 0.049$) and vigorous physical activity for

more than an hour ($p = 0.001$), compared to those with a BMI of 25–29.99 who undertook these physical activity levels (Figure 1).

There was no evidence of heterogeneity across centres in the meta-analyses.

Discussion

In this study of middle-aged adults, increasing frequency of lighter physical activity, but not vigorous activity, was a predictor of less current asthma (wheeze without cold, asthma attacks/asthma medications) over ten years. These associations were attenuated after BMI adjustment and no longer statistically significant. We could identify no association between physical activity and incident asthma over ten years. In the all-centre cross-sectional study, there was no association between physical activity and current asthma; however, there was an interaction between physical activity and BMI, indicating that those with normal BMI experienced a reduction in asthma

symptoms associated with physical activity while those with a higher BMI did not.

The positive effect from physical activity on current asthma was attenuated by BMI adjustment in this study. This may indicate that BMI is a confounder in the association or that BMI may be a mediator of the association. Support for BMI as a mediator can be found in the biological explanations of the associations between physical activity and BMI [22–25] and also in RCTs demonstrating that physical activity can alter asthma outcomes [4,5]. Concomitantly, a number of pathophysiological mechanisms of how physical activity effects asthma, with and without BMI mediation, have been suggested. Physical activity has been found to improve insulin sensitivity [26] and that hyperinsulinaemia may stimulate asthma through increasing Type 2 helper T cell responses and airway hyper-responsiveness [27]. Considering possible BMI mediation, the adipose tissue-secreted adipokines (leptin and adiponectin) may influence insulin sensitivity [28] and potentially asthma [22]. Other possible

Table 2. RHINE II–RHINE III Bergen longitudinal analysis: RHINE II frequency of light physical activity and frequency of vigorous physical activity as predictors of RHINE III current asthma, asthma symptoms and asthma incidence.

	Asthma outcome			
	Absent, <i>n</i> (%)	Present, <i>n</i> (%)	Adjusted odds ratio (95%CI) ^a	Adjusted odds ratio (95%CI) ^b
Current asthma				
<i>Frequency of physical activity per week</i>				
None	240 (15)	28 (28)	1.00	1.00
Lighter activity 1–2	470 (30)	27 (27)	0.65 (0.31, 1.35)	0.70 (0.33, 1.47)
Lighter activity 3+	884 (55)	45 (45)	0.44 (0.22, 0.89) ^d	0.50 (0.24, 1.02)
<i>p</i> for linear trend			0.021 ^d	0.051
None	751 (49)	52 (56)	1.00	1.00
Vigorous activity 1–2	559 (36)	26 (28)	1.12 (0.62, 2.06)	1.22 (0.66, 2.26)
Vigorous activity 3+	234 (15)	15 (16)	1.22 (0.55, 2.76)	1.51 (0.66, 3.44)
<i>p</i> for linear trend			0.587	0.304
Incident asthma				
<i>Frequency of physical activity per week</i>				
None	227 (16)	8 (15)	1.00	1.00
Lighter activity 1–2	417 (29)	15 (28)	1.37 (0.51, 3.69)	1.36 (0.50, 3.71)
Lighter activity 3+	793 (55)	30 (56)	1.25 (0.48, 3.24)	1.41 (0.54, 3.69)
<i>p</i> for linear trend			0.851	0.576
None	672 (48)	27 (54)	1.00	1.00
Vigorous activity 1–2	513 (37)	16 (32)	0.75 (0.38, 1.46)	0.76 (0.39, 1.49)
Vigorous activity 3+	209 (15)	7 (14)	1.03 (0.42, 2.49)	0.89 (0.34, 2.30)
<i>p</i> for linear trend			0.774	0.607
Asthma symptoms			Adjusted rate ratio (95% CI) ^a	Adjusted rate ratio (95% CI) ^b
<i>Frequency of physical activity per week</i>				
None	147 (14)	117 (19) ^c	1.00	1.00
Lighter activity 1–2	317 (30)	176 (28) ^c	0.88 (0.73, 1.06)	0.88 (0.73, 1.06)
Lighter activity 3+	592 (56)	327 (53) ^c	0.86 (0.72, 1.02)	0.84 (0.70, 1.00)
<i>p</i> for linear trend			0.116	0.060
None	493 (47)	300 (52) ^c	1.00	1.00
Vigorous activity 1–2	383 (37)	193 (34) ^c	1.00 (0.86, 1.16)	1.02 (0.87, 1.18)
Vigorous activity 3+	166 (16)	81 (14) ^c	0.96 (0.78, 1.18)	1.06 (0.86, 1.30)
<i>p</i> for linear trend			0.753	0.610

Notes. CI, confidence interval.

^a Adjusted for age, gender, smoking status, educational level and RHINE II current asthma in the current asthma outcome analyses, RHINE II asthma symptoms in the asthma symptoms outcome analysis.

^b Adjusted for the previous factors and RHINE II BMI as a categorical variable.

^c Present n (%): indicates one or more asthma symptoms present.

^d $p < 0.05$.

Table 3. RHINE III all-centre cross-sectional study: association between RHINE III physical activity and RHINE III current asthma and asthma symptoms.

	Asthma outcome		Adjusted odds ratio (95% CI) ^a	Adjusted odds ratio (95% CI) ^b
	Absent, n (%)	Present, n (%)		
Current asthma				
Physical activity per week:				
None	2,704 (23)	221 (32)	1.00	1.00
Light, ≤1 hour	1,692 (14)	91 (13)	0.78 (0.54, 1.13)	0.83 (0.57, 1.19)
Light, >1 hour	4,061 (34)	193 (28)	0.79 (0.59, 1.06)	0.83 (0.61, 1.11)
Vigorous, ≤1 hour	1,079 (9)	50 (7)	0.57 (0.36, 0.91) ^d	0.64 (0.39, 1.02)
Vigorous, >1 hour	2,456 (20)	144 (20)	0.96 (0.70, 1.31)	1.06 (0.77, 1.47)
Likelihood ratio test <i>p</i> value			0.100	0.157
Asthma symptoms			Adjusted rate ratio (95% CI) ^a	Adjusted rate ratio (95% CI) ^e
Physical activity per week				
None	1,520 (55)	1,235 (45) ^c	1.00	
Light, ≤1 hour	1,029 (60)	687 (40) ^c	0.96 (0.89, 1.03)	
Light, >1 hour	643 (59)	442 (41) ^c	0.90 (0.75, 1.08)	
Vigorous, ≤1 hour	2,634 (64)	1,503 (36) ^c	0.92 (0.86, 0.98) ^d	
Vigorous, >1 hour	1,641 (65)	887 (35) ^c	0.99 (0.93, 1.08)	
Wald test <i>p</i> value			0.009 ^d	

Note. CI, confidence interval.

^a Each analysis adjusted for age, gender, RHINE III smoking, educational level and RHINE II current asthma in the current asthma analysis, and RHINE II report of asthma symptoms in the asthma symptom analysis.

^b Adjusted for the previous factors and RHINE III BMI as a categorical variable.

^c Present, *n* (%): indicates one or more asthma symptoms present.

^d *p* < 0.05.

^e No adjustment for BMI in the presence of the interaction.

obesity-asthma mechanisms are the effect of weight on lung mechanics, gastro-oesophageal reflux and obstructive sleep apnoea [29]. Overall, there are plausible pathways through which physical activity may influence asthma as an independent factor or through BMI mediation; however, it should not be discounted that the physical activity and asthma associations may be due to BMI confounding.

An intriguing finding seen in the longitudinal study was the positive effect on current asthma from lighter activity but a trend towards a negative effect from vigorous activity. An increased risk of asthma from vigorous activity has been reported in cross-sectional studies [30–32] and studies of athletes [33–36] previously. The trend towards an increased risk with vigorous activity may be due to exercise induced bronchoconstriction, complicated by the effect of breathing cold dry air in Scandinavian winter sport activities [36,37]. However, without further information about the type of exercise (i.e. endurance/resistance or indoor/outdoor) it is difficult to speculate as to the cause of the trend.

In the all-centre cross-sectional study, an interaction demonstrated that more physical activity was associated with reduced asthma symptoms in normal BMI participants but not overweight participants. It is important to remember that as a cross-sectional analysis this result could be interpreted as overweight people with asthma symptoms being less likely to be physically active, and a previous study of adolescents concluded this from similar

results [38]. Without knowing the temporal relationship, the direction of the association can only be speculated.

No significant effect of physical activity on asthma incidence was found. Some previous studies have also found no association [10,11], whilst other studies have found an effect [7,39]. A common factor in the studies finding an association was no mention of confounding adjustment. In our analysis, a limitation was low statistical power. Overall, more research is required to discern trends.

The strengths of this study are its long-term follow-up and comparison across study designs. A weakness is that physical activity was self-reported and as such prone to overestimation by participants [40]. This is likely to result in the underestimation of the associations observed. Additionally, the light and vigorous physical activity questions make it difficult to discern the effect from moderate physical activity or consider the duration and type of activity. The asthma outcomes were also self-reported and hence there is a risk that other morbidities may present with similar symptoms; this may amplify the association observed if physical activity is protective for these conditions. A further weakness is possible reverse causality, with previous levels of asthma (e.g. childhood asthma) and obesity potentially influencing physical activity. To address this, we undertook a sensitivity analysis with adjustment for RHINE I asthma and BMI and found no change in associations. Loss to follow-up is a potential consideration; however, there was no interaction between the RHINE II factors and loss. It also should be noted that

the association between physical activity and asthma may be different in this European population where physical activity may be prevalent and average BMI lower than, for example, in North America [41].

Current Global Initiative for Asthma guidelines state that there is no evidence that physical activity has an effect on asthma, but encourages people with asthma to be physically active for a general health benefit [42]. This research indicates that physical activity over the longer term may have an effect on asthma and that there may be an absence of increased benefit from increased physical activity intensity. Additionally, this study highlights the potential complex nature of the association between physical activity, BMI and asthma. It may be that physical activity is only effective in reducing asthma symptoms in people with a normal BMI; however other large studies will be required to explore this.

Conclusion

In this study, lighter physical activity was found to reduce current asthma in middle-aged adults over time, whilst benefit from increasing intensity of physical activity was not evident over time. After adjustment for BMI the association was no longer significant. Cross-sectionally at different levels of BMI, the association between physical activity and asthma differed. These results indicate the complex association between physical activity, BMI and asthma, with the possibility that the benefit from physical activity may differ according to BMI.

Acknowledgements

The authors thank the RHINE staff and study participants.

Declaration of interest

The authors declare that there are no conflicts of interest. The authors alone are responsible for the writing and content of the paper.

Funding

RHINE was supported financially by the Norwegian Research Council (Grant Nos. 214123, 912011), the Bergen Medical Research Foundation, the Western Norwegian Regional Health Authorities (Grant No. 911 892 and 911 631), the Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association, the Faculty of Health of Aarhus University (Project No. 240008), the Wood Dust Foundation (Project No. 444508795), the Danish Lung Association, the Swedish Heart and Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish Council for Working Life and Social Research, the Bror Hjerpstedt Foundation, the Swedish

Asthma and Allergy Association, the Icelandic Research Council, and the Estonian Science Foundation (Grant No. 4350). S Dharmage is supported by an NHMRC.

ORCID

Cecilie Svanes  <http://orcid.org/0000-0001-8512-5192>

References

1. Nocon M, Hiemann T, Mueller-Riemenschneider F, Thallau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehab* 2008;15(3):239–246.
2. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Does regular physical activity reduce lung function decline and COPD risk among smokers? *Am J Resp Crit Care* 2007;176(3):314–315.
3. Smidt N, de Vet HCW, Bouter LM, Dekker J, Exercise Therapy G. Effectiveness of exercise therapy: a best-evidence summary of systematic reviews. *Aust J Physiother* 2005;51(2):71–85.
4. Heikkinen SAM, Quansah R, Jaakkola JJK, Jaakkola MS. Effects of regular exercise on adult asthma. *Eur J Epidemiol* 2012;27(6):397–407.
5. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. *Cochrane Database Syst Rev* 2013;9:CD001116.
6. Huovinen E, Kaprio J, Koskenvuo M. Factors associated to lifestyle and risk of adult onset asthma. *Respir Med* 2003;97(3):273–280.
7. Lucke J, Waters B, Hockey R, Spallek M, Gibson R, Byles J, et al. Trends in women's risk factors and chronic conditions: findings from the Australian Longitudinal Study on Women's Health. *Women's Health (Lond Engl)*. 2007;3(4):423–432.
8. Garcia-Aymerich J, Varraso R, Anto JM, Camargo CA. Prospective study of physical activity and risk of asthma exacerbations in older women. *Am J Resp Crit Care* 2009;179(11):999–1003.
9. Shaaban R, Leynaert B, Soussan D, Anto JM, Chinn S, de Marco R, et al. Physical activity and bronchial hyper-responsiveness: European Community Respiratory Health Survey II. *Thorax* 2007;62(5):403–410.
10. Benet M, Varraso R, Kauffmann F, Romieu I, Anto JM, Clavel-Chapelon F, et al. The effects of regular physical activity on adult-onset asthma incidence in women. *Respir Med* 2011;105(7):1104–1107.
11. Beckett WS, Jacobs DR, Yu XH, Iribarren C, Williams D. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Resp Crit Care* 2001;164(11):2045–2050.
12. Eijkemans M, Mommers M, Draaisma JMT, Thijs C, Prins MH. Physical activity and asthma: a systematic review and meta-analysis. *Plos ONE* 2012;7(12).
13. Johannessen A, Verlato G, Benediktsdottir B, Forsberg B, Franklin K, Gislason T, et al. Longterm follow-up in European respiratory health studies – patterns and implications. *BMC Pulm Med* 2014;14.
14. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the

- Nord-Trondelag Health Study – HUNT 1. *Scand J Public Health* 2008;36(1):52–61.
15. Gislason T, Bertelsen RJ, Real FG, Sigsgaard T, Franklin KA, Lindberg E, et al. Self-reported exposure to traffic pollution in relation to daytime sleepiness and habitual snoring: a questionnaire study in seven North-European cities. *Sleep Med* 2016;24:93–99.
 16. Holmen H, Wahl A, Torbjornsen A, Jenum AK, Smastuen MC, Ribu L. Stages of change for physical activity and dietary habits in persons with type 2 diabetes included in a mobile health intervention: the Norwegian study in RENEWING HEALTH. *BMJ Open Diabetes Res Care* 2016;4(1):e000193.
 17. Ellekjaer H, Holmen J, Ellekjaer E, Vatten L. Physical activity and stroke mortality in women. Ten-year follow-up of the Nord-Trondelag health survey, 1984–1986. *Stroke* 2000;31(1):14–18.
 18. Woodhouse A, Pape K, Romundstad PR, Vasseljen O. Health care contact following a new incident neck or low back pain episode in the general population; the HUNT study. *BMC Health Serv Res* 2016;16:81.
 19. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *Eur Respir J* 1996;9:687–695.
 20. Pekkanen J, Sunyer J, Anto JM, Burney P, Ecrhs. Operational definitions of asthma in studies on its aetiology. *Eur Respir J* 2005;26(1):28–35.
 21. Lee AH, Wang K, Scott JA, Yau KKW, McLachlan GJ. Multi-level zero-inflated Poisson regression modelling of correlated count data with excess zeros. *Stat Methods Med Res* 2006;15(1):47–61.
 22. Kim SH, Sutherland ER, Gelfand EW. Is there a link between obesity and asthma? *Allergy Asthma Immunol Res* 2014;6(3):189–195.
 23. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol Rev* 2012;92(1):157–191.
 24. Conn VS, Hafdahl A, Phillips LJ, Ruppert TM, Chase JA. Impact of physical activity interventions on anthropometric outcomes: systematic review and meta-analysis. *J Prim Prev* 2014;35(4):203–215.
 25. Brashier B, Salvi S. Obesity and asthma: physiological perspective. *J Allergy (Cairo)* 2013;2013:198068.
 26. Balkau B, Mhamdi L, Oppert JM, Nolan J, Golay A, Porcellati F, et al. Physical activity and insulin sensitivity: the RISC study. *Diabetes* 2008;57(10):2613–2618.
 27. Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy (Cairo)* 2013;2013:627384.
 28. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta* 2013;417:80–84.
 29. Novosad S, Khan S, Wolfe B, Khan A. Role of obesity in asthma control, the obesity-asthma phenotype. *J Allergy (Cairo)* 2013;2013:538642.
 30. Jerning C, Martinander E, Bjerg A, Ekerljung L, Franklin KA, Jarvholm B, et al. Asthma and physical activity – a population based study results from the Swedish GA(2)LEN survey. *Respir Med* 2013;107(11):1651–1658.
 31. Verlaet A, Moreira A, Sa-Sousa A, Barros R, Santos R, Moreira P, et al. Physical activity in adults with controlled and uncontrolled asthma as compared to healthy adults: a cross-sectional study. *Clin Transl Allergy* 2013;3(1):1.
 32. Uddenfeldt M, Janson C, Lampa E, Leander M, Norback D, Larsson L, et al. High BMI is related to higher incidence of asthma, while a fish and fruit diet is related to a lower - results from a long-term follow-up study of three age groups in Sweden. *Respir Med* 2010;104(7):972–980.
 33. Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998;101(5):646–652.
 34. Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Akdis C, et al. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. *Curr Opin Allergy Clin Immunol* 2015;15(2):184–192.
 35. Carlsen KH, Anderson SD, Bjerner L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. *Allergy* 2008;63(4):387–403.
 36. Langdeau JB, Turcotte H, Bowie DM, Jobin J, Desgagne P, Boulet LP. Airway hyperresponsiveness in elite athletes. *Am J Resp Crit Care* 2000;161(5):1479–1484.
 37. Kippelen P, Anderson SD. Pathogenesis of exercise-induced bronchoconstriction. *Immunol Allergy Clin North Am* 2013;33(3):299+.
 38. Lawson JA, Rennie DC, Dosman JA, Cammer AL, Senthilselvan A. Obesity, diet, and activity in relation to asthma and wheeze among rural dwelling children and adolescents. *J Obes* 2013;2013:315096.
 39. Thomsen SF, Ulrik CS, Kyvik KO, Larsen K, Skadhauge LR, Steffensen IE, et al. Risk factors for asthma in young adults: a co-twin control study. *Allergy* 2006;61(2):229–233.
 40. Helmerhorst HJF, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *Int J Behav Nutr Phys Act* 2012;9.
 41. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* 2012;380(9838):247–257.
 42. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention 2015. Available from: www.ginasthma.org

Physical activity and asthma: a longitudinal and multi-country study

Author Information

Melissa A Russell ^{a,b}, Christer Janson ^c, Francisco Real ^{d,e}, Ane Johannessen ^f, Marie Waatevik ^g,
Bryndis Benediktsdóttir ^{h,i}, Mathias N Holm ^j, Eva Lindberg ^c, Vivi Schlünssen ^{k,l}, Wasif Raza ^m,
*Shyamali C Dharmage ^{a,b} and *Cecile Svanes ^{f,n}

Affiliations

- a. Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, Australia.*
- b. Gastro & Food Allergy Group, Murdoch Children's Research Institute, Melbourne, Australia.*
- c. Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden.*
- d. Department of Clinical Science, University of Bergen, Bergen, Norway.*
- e. Department of Gynaecology and Obstetrics, Haukeland University Hospital, Bergen, Norway.*
- f. Center for International Health, University of Bergen, Bergen, Norway.*
- g. Center for Clinical Research, Haukeland University Hospital, Bergen, Norway.*
- h. Faculty of Medicine, University of Iceland, Reykjavik, Iceland.*
- i. Department of Respiratory Medicine and Sleep, The National University Hospital of Iceland, Reykjavik, Iceland.*

- j. *Department of Occupational and Environmental Medicine, Sahlgrenska University Hospital, Göteborg, Sweden.*
- k. *Department of Public Health, Aarhus University, Aarhus, Denmark.*
- l. *Department of Occupational Medicine, Danish Ramazzini Centre, Aarhus University Hospital, Aarhus, Denmark.*
- m. *Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.*
- n. *Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway.*

***SD and CS are equal contributing authors**

Corresponding author:

Email melissar@unimelb.edu.au (MR)

Telephone 61 3 83440736

Physical activity and asthma: a longitudinal and multi-country study

Key words: physical exercise, asthma, adult, RHINE

ABSTRACT

Objective: To investigate the impact of physical activity on asthma in middle-aged adults, in one longitudinal analysis, and one multi-centre cross-sectional analysis.

Methods: The Respiratory Health in Northern Europe (RHINE) is a population based postal questionnaire cohort study. Physical activity, height and weight were self-reported in Bergen, Norway, at RHINE II (1999-2001) and all centres at RHINE III (2010-2012). A longitudinal analysis of Bergen data investigated the association of baseline physical activity with follow-up current asthma, incidence and symptoms using logistic and zero-inflated poisson regression (n=1782). A cross-sectional analysis of all RHINE III centres investigated the association of physical activity with concurrent asthma and symptoms (n=13,542) using mixed effects models. Body mass index (BMI) was categorised (<20, 20-24.99, 25-29.99, 30+ kg/m²) and physical activity grouped by amount and frequency of lighter (no sweating/heavy breathing) and vigorous (sweating/heavy breathing) activity.

Results: In the Bergen longitudinal analysis undertaking light activity 3+ times/week at baseline was associated with less follow-up asthma (odds ratio [OR] 0.44, 95% Confidence Interval [CI] 0.22, 0.89), whilst an effect from undertaking vigorous activity 3+ times/week was not detected (OR 1.22, 95%CI 0.44, 2.76) . The associations were attenuated with BMI adjustment. In the all-centre cross-sectional analysis an interaction was found, with the association between physical activity and asthma varying across BMI categories.

Conclusion: These findings suggest potential longer-term benefit from lighter physical activity, whilst improvement in asthma outcomes from increasing activity intensity was not evident. Additionally, it appears the benefit from physical activity may differ according to BMI.

INTRODUCTION

There is growing interest in the role of physical activity in the aetiology and prognosis of asthma. Physical activity is an attractive option in the management of asthma as it is modifiable, has complimentary health benefits (1), and has shown to be beneficial for other chronic respiratory conditions (2, 3).

Systematic reviews of randomised controlled trials (RCTs) have indicated improvement in cardiopulmonary fitness and quality of life from exercise interventions (4, 5); however the longer-term effects on asthma are less well established. Longitudinal studies show mixed results; some studies suggesting that physical activity is associated with improved asthma outcomes (6-9), while other studies have found no such associations (10, 11). Most of the observational research is cross-sectional (12), with the methodological challenges of reverse causality (i.e. does physical activity precede asthma or vice versa). The role of obesity as a confounder or mediator adds to the complexity. Larger population studies are required to determine the effect of physical activity over time on asthma incidence and prognosis, and also explore the role of obesity.

The population-based Respiratory Health in Northern Europe (RHINE) study provided an opportunity to investigate the impact of physical activity on multiple asthma outcomes in middle-aged adults, whilst taking into account body mass index (BMI). The objective of this study was to investigate the effect of physical activity on asthma incidence, prevalence and symptoms, in separate longitudinal and cross-sectional analyses. We hypothesised increased physical activity would be associated with (1) lower asthma incidence and less asthma prevalence and, symptoms over ten years, and (2) less concurrent asthma and asthma symptoms consistently across geographical borders.

MATERIAL AND METHODS

Study population

RHINE is a population-based cohort from seven Northern European centres that includes a randomly selected sample of men and women, born 1945-73, from Reykjavik, Iceland; Bergen, Norway; Umeå, Uppsala and Goteborg, Sweden; Aarhus, Denmark; and Tartu, Estonia. In 1991-1993 21,659 persons responded to a postal screening survey as part of the European Community Respiratory Health Survey I/RHINE 1, and this cohort was resurveyed in 1999-2001 (RHINE II; 16,106 participants / 75%), and 2010-12 (RHINE III, 11,441 participants / 53%) (13). The questions included in the postal survey were translated and back-translated into local languages at each of the centres and the co-ordinating centre then checked all back-translations.

Local ethics committees approved the study and all participants consented to participate.

Participants were excluded from analyses if they reported a doctor diagnosis of Chronic Obstructive Pulmonary Disease (COPD).

RHINE II –RHINE III Bergen longitudinal study

Physical activity was recorded only in Bergen in RHINE II and for the purposes of this analysis compared to the asthma outcomes at RHINE III. The Bergen cohort included 3449 participants in RHINE I, with 2506 participants (73%), and 1833 participants (53%) in subsequent follow-ups (13).

RHINE III all center cross-sectional study

Physical activity was recorded in all centres in RHINE III and for the purposes of this analysis compared cross-sectionally to asthma outcomes across all centres.

Physical activity

In RHINE II Bergen, physical activity was recorded in two questions regarding (1) frequency of lighter activity (no sweating/no heavy breathing), and (2) frequency of vigorous activity (sweating/ heavy breathing); response alternatives 0, <1, 1-2 or 3+ times per week. For each question the lowest two response alternatives were collapsed and defined as "no physical activity" as it was reasoned that there was little material difference between the two categories. The type of physical activity undertaken and length of physical activity sessions was not recorded. Hence, we defined two physical activity variables, 'frequency of lighter physical activity' and 'frequency of vigorous physical activity', each with three levels (0, 1-2, or 3+ times per week).

In RHINE III physical activity was collected across three questions regarding: (1) frequency, (2) intensity, and (3) length of physical activity sessions. These questions have been found to be reliable and correlated with VO2 max (14), and have been used previously in RHINE publications (15) and in many investigations from the Nord-Trøndelag Health (HUNT) study (16-18) . A categorical variable was created by ranking combinations of these questions and then dividing according to the median time spent physically active (1 hour) and whether the activity

was light or vigorous (see online supplement). This resulted in five categories of the variable “physical activity per week”: no physical activity, ≤ 1 hour light, >1 hour light, ≤ 1 hour vigorous, and >1 hour vigorous. It should be noted that it was not possible to produce a physical activity variable with the same categories across RHINE II and RHINE III.

Asthma outcomes

Current asthma

Participants reporting at least two of the following three issues were classified as having current asthma: “an attack of asthma in the last 12 months” , “taking any medicine (including inhalers, aerosols or tablets) for asthma in the past 12 months” and/or “whistling or wheezing in the chest at any time during the last 12 months when you have not had a cold” (19).

Asthma Symptoms

An asthma symptoms count variable, scored 0 to 8, was formed from answers to eight questions regarding wheeze, wheeze with shortness of breath, wheeze without cold, waking with tightness in chest, waking with shortness of breath, waking with cough, asthma attacks the last 12 months, and current asthma medication (20). For each “yes” a score of one was given.

Incident asthma

Incident asthma was obtained from the answers to the RHINE III questions “Do you have or have you ever had asthma?” and “How old were you when you first experienced asthma symptoms?” If participants responded that they had ever asthma in RHINE III but not RHINE II and the age of first experiencing asthma symptoms was between RHINE II and RHINE III they were classed as having incident asthma and were compared to the control group of those reporting never asthma in RHINE III. To exclude those who had a history of asthma participants who reported “ever asthma” in RHINE II or onset of symptoms prior to RHINE II were excluded.

Confounders

Confounders considered were gender, age (continuous), smoking, education (primary, secondary or university/college), previous asthma status and BMI. Smoking was grouped into eight categories (see online supplement). BMI was based on self-reported height and weight and categorised (<20 , 20-24.99, 25-29.99 and 30+ kg/m²) to take into account any non-linear associations.

Analysis

RHINE II –RHINE III Bergen longitudinal study

Three longitudinal analyses were undertaken in the RHINE II–RHINE III Bergen cohort between baseline (RHINE II) ‘frequency of lighter physical activity’ and ‘frequency of vigorous activity’ and the follow-up (RHINE III) asthma outcome variables (‘current asthma’, ‘asthma symptoms’, and ‘incident asthma’). The two physical activity variables were entered into the analyses concurrently, so the effect of each could be observed whilst adjusting for the other. Gender, age, education, RHINE II smoking and the related baseline asthma variable (i.e. RHINE II current asthma when RHINE III current asthma was the outcome) were identified as confounders using directed acyclic graphs (DAGs) and added to the models. Baseline (RHINE II) categorical BMI was added separately to each model to observe BMI as being on the causal pathway/a potential confounder.

Logistic regression was used with ‘current asthma’, and ‘incident asthma’ outcomes. Zero inflated poisson regression was used for the analysis with the outcome ‘asthma symptoms’, a count variable with excess zeroes (21). Interactions between each physical activity variable and gender, age, RHINE II asthma baseline variables and RHINE II BMI were considered.

The Bergen longitudinal study had 30% power, at a 5% significance level, to detect a reduction in the odds of current asthma of 0.88 (12) for those undertaking any level of physical activity compared to the base category. Sensitivity analyses were undertaken to investigate (1) reverse causation (analyses adjusting for RHINE I BMI and asthma) (2) and predictors of loss to follow up (see online supplement for further details).

RHINE III all center cross-sectional study

Two cross-sectional analyses were undertaken between RHINE III ‘physical activity per week’ and RHINE III ‘current asthma’, and ‘asthma symptoms’. The confounders of gender, age, education, RHINE III smoking and the related baseline asthma variable were identified in a DAG and adjusted for. RHINE III BMI was added separately to each model to observe BMI as being on the causal pathway/a potential confounder. Multilevel mixed effect models for binary outcomes, with two levels and a random intercept was used with ‘current asthma’ as the outcome, to take into account center clustering. Zero inflated poisson regression, with standard errors allowing for clustering, was used with asthma symptoms as the outcome. Interactions between physical activity per week and gender, age, RHINE II asthma baseline variables and RHINE III BMI were considered. When significant interactions were identified the effect of physical activity was stratified across the modifying term and presented graphically.

We also undertook a random effects meta-analysis to investigate heterogeneity in effects across centres. STATA 13 (StataCorp, College Station Texas) was used.

RESULTS

Participant characteristics

In RHINE II –RHINE III Bergen longitudinal study 1,782 participants were available for analyses after excluding 29 participants with COPD. With exclusion of those with asthma at baseline, incident asthma was analysed in 1,573 participants. Participant characteristics are available in Supplementary Table 1.

In the RHINE III all centre cross-sectional analysis 13,542 participants were available for analyses, after excluding 358 participants with COPD. Seven percent of participants had current asthma (Table 1) and the median number of asthma symptoms was 0 (Interquartile Range [IQR] 0-1). Age and sex were evenly distributed across centres, and current asthma was most prevalent in Umeå and Uppsala (Table 1).

Physical activity

In the RHINE II-RHINE III Bergen longitudinal study 406 (17.3%), 697 (29.7%), and 1246 (53.0%) participants reported no, 1-2, and 3+ sessions of lighter physical activity per week, respectively, and 1134 (50.1%), 787 (34.8%) and 341 (15.1%) participants reported no, 1-2, and 3+ sessions of vigorous physical activity per week respectively, at baseline.

In the RHINE III all center cross-sectional study 2,864 (23.0%) participants reported no physical activity per week and most frequently participants reported less than an hour of vigorous activity per week (4,269 participants, 34%) (Table 1).

Table 1. Characteristics of participants in the RHINE III study across centers. Data are presented as n (%) unless otherwise specified.

Centre	Aarhus (n=2268)	Reykjavik (n=2161)	Bergen (n=2314)	Goteberg (n=1690)	Umeå (n=1922)	Uppsala (n=1911)	Tartu (n=1276)	Total ^a (13,542)
Mean age [95%CI]	50 [50, 50]	53 [53, 54]	51 [51, 51]	53 [52, 53]	53 [53, 53]	53 [52, 53]	49 [48, 49]	52 [52, 52]
Female	1,197 (53)	941 (53)	1,160 (50)	899 (53)	1,008 (53)	994 (52)	741 (58)	6,940 (53)
Never smoked	1,016 (45)	678 (40)	892 (39)	796 (48)	1,073 (57)	1,085 (58)	440 (47)	5,980 (48)
Current asthma	92 (4.1)	121 (6.3)	141 (6.1)	94 (5.6)	119 (6.3)	113 (5.9)	44 (3.5)	724 (5.5)
Incident asthma ^b	41 (2.3)	62 (4.6)	55 (3.4)	21 (1.6)	35 (2.3)	35 (3.7)	16 (3.7)	265 (2.8)
Mean BMI kg/m ² (95%CI]	25 [25, 25]	27 [27, 27]	26 [26, 26]	26 [26, 26]	26 [26, 26]	26 [26, 26]	27 [26, 27]	26 [25, 26]
Physical Activity per week								
None	498 (23)	559 (34)	411 (18)	403 (25)	321 (17)	405 (22)	267 (23)	2,864 (23)
Lighter, ≤1 hour	301 (14)	164 (9.3)	269 (12)	242 (15)	307 (16)	261 (14)	251 (21)	1,785 (14)
Lighter, > 1 hour	219 (9.9)	73 (4.4)	177 (7.8)	134 (8.2)	212 (11)	184 (9.9)	138 (12)	1,137 (9.0)
Vigorous, ≤1 hour	775 (35)	543 (33)	802 (35)	575 (35)	609 (33)	696 (38)	269 (23)	4,269 (34)
Vigorous, > 1 hour	415 (19)	334 (20)	614 (27)	287 (18)	420 (23)	309 (17)	234 (20)	2,613 (21)

CI: Confidence Interval BMI: Body Mass Index

a Number of participants with missing data: 1082 for age, 411 for gender, 939 for smoking history, 664 for BMI, 484 for education, 498 for current asthma, 875 for asthma symptoms, 532 for wheeze, 874 for physical activity per week.

b Participants excluded because a history of asthma was recorded in RHINE II and/or age of onset of asthma symptoms was prior to RHINE II.

RHINE II –RHINE III Bergen longitudinal study

There was a statistically significant linear trend for a protective effect from increasing frequency of lighter physical activity in regard to current asthma, after adjustment for a priori defined confounders ($p_{\text{trend}}=0.021$) (Table 2). This association was attenuated after BMI adjustment ($p_{\text{trend}}=0.051$). There was no significant association between vigorous activity at baseline and current asthma at follow up. There was a modest non-significant trend towards increased odds of current asthma with undertaking vigorous activity 3+ times per week after adjustment for BMI (Odds Ratio [OR]: 1.51, 95% Confidence interval [CI] 0.66, 3.44).

There was no association between the frequency of lighter or vigorous physical activity at baseline and number of asthma symptoms at follow-up or incident asthma (Table 2).

In the sensitivity analysis there was no material difference with the RHINE I current asthma and RHINE I BMI added into the analyses. Some RHINE II factors were associated with loss to follow up; however there was no interaction between the physical activity variables and RHINE II asthma factors in predicting loss to follow up (Supplement 1).

Table 2. RHINE II –RHINE III Bergen longitudinal analysis: RHINE II frequency of light physical activity and frequency of vigorous physical activity as predictors of RHINE III current asthma/wheeze, asthma symptoms and asthma incidence.

	Asthma Outcome		Adjusted odds ratio (95%CI) ^a	Adjusted odds ratio (95%CI) ^b
	Absent, n (%)	Present, n (%)		
Current asthma				
<i>Frequency of physical activity per week:</i>				
None	240 (15)	28 (28)	1.00	1.00
Lighter activity 1-2	470 (30)	27 (27)	0.65 (0.31, 1.35)	0.70 (0.33, 1.47)
Lighter activity 3+	884 (55)	45 (45)	0.44 (0.22, 0.89) ^d	0.50 (0.24, 1.02)
p for linear trend			0.021 ^d	0.051
None	751 (49)	52 (56)	1.00	1.00
Vigorous activity 1-2	559 (36)	26 (28)	1.12 (0.62, 2.06)	1.22 (0.66, 2.26)
Vigorous activity 3+	234 (15)	15 (16)	1.22 (0.55, 2.76)	1.51 (0.66, 3.44)
p for linear trend			0.587	0.304
Incident asthma				
<i>Frequency of physical activity per week:</i>				
None	227 (16)	8 (15)	1.00	1.00
Lighter activity 1-2	417 (29)	15 (28)	1.37 (0.51, 3.69)	1.36 (0.50, 3.71)
Lighter activity 3+	793 (55)	30 (56)	1.25 (0.48, 3.24)	1.41 (0.54, 3.69)
p for linear trend			0.851	0.576

None	672 (48)	27 (54)	1.00	1.00
Vigorous activity 1-2	513 (37)	16 (32)	0.75 (0.38, 1.46)	0.76 (0.39, 1.49)
Vigorous activity 3+	209 (15)	7 (14)	1.03 (0.42, 2.49)	0.89 (0.34, 2.30)
p for linear trend			0.774	0.607
Asthma symptoms			Adjusted rate ratio (95% CI) ^a	Adjusted rate ratio (95% CI) ^b
<i>Frequency of physical activity per week:</i>				
None	147 (14)	117 (19) ^c	1.00	1.00
Lighter activity 1-2	317 (30)	176 (28) ^c	0.88 (0.73, 1.06)	0.88 (0.73, 1.06)
Lighter activity 3+	592 (56)	327 (53) ^c	0.86 (0.72, 1.02)	0.84 (0.70, 1.00)
p for linear trend			0.116	0.060
None	493 (47)	300 (52) ^c	1.00	1.00
Vigorous activity 1-2	383 (37)	193 (34) ^c	1.00 (0.86, 1.16)	1.02 (0.87, 1.18)
Vigorous activity 3+	166 (16)	81 (14) ^c	0.96 (0.78, 1.18)	1.06 (0.86, 1.30)
p for linear trend			0.753	0.610

CI: Confidence Interval

a Adjusted for age, gender, smoking status, educational level and RHINE II current asthma in the current asthma outcome analyses, RHINE II asthma symptoms in the asthma symptoms outcome analysis.

b Adjusted for the previous factors and RHINE II BMI as a categorical variable.

c Present n (%): indicates one or more asthma symptoms present.

d $p < 0.05$

RHINE III all center cross-sectional study

Physical activity per week and current asthma were not significantly associated in the RHINE III all center cross-sectional study before ($p=0.100$) and after ($p=0.157$) adjustment for BMI (Table 3).

There was a significant decrease in the number of asthma symptoms when undertaking less than one hour of vigorous physical activity (RR 0.90 95% CI 0.84, 0.96, $p=0.002$) compared to no physical activity, after adjustment for a priori defined confounders (Table 3). There was an interaction between physical activity and BMI with asthma symptoms as the outcome (Figure 1). It demonstrated that there was a significant decrease in asthma symptoms for participants with a RHINE III BMI of 20 to 24.99 who undertook light physical activity for an hour or more per week ($p=0.045$), vigorous physical activity less than an hour ($p=0.049$) and vigorous physical activity for more than an hour ($p=0.001$), compared to those with a BMI of 25 to 29.99 who undertook these physical activity levels (Figure 1).

There was no evidence of heterogeneity across centers in the meta-analyses.

Table 3: RHINE III-all center cross-sectional study: association between RHINE III physical activity and RHINE III current asthma, wheeze and asthma symptoms.

	Asthma Outcome		Adjusted odds	Adjusted odds
	Absent, n (%)	Present, n (%)	ratio (95 %CI)^a	ratio (95%CI)^b
Current asthma				
<i>Physical activity per week:</i>				
None	2,704 (23)	221 (32)	1.00	1.00
Light, ≤1 hour	1,692 (14)	91 (13)	0.78 (0.54, 1.13)	0.83 (0.57, 1.19)
Light, > 1 hour	4,061 (34)	193 (28)	0.79 (0.59, 1.06)	0.83 (0.61, 1.11)
Vigorous, ≤1 hour	1,079 (9)	50 (7)	0.57 (0.36, 0.91) ^d	0.64 (0.39, 1.02)
Vigorous, > 1 hour	2,456 (20)	144 (20)	0.96 (0.70, 1.31)	1.06 (0.77, 1.47)
Likelihood ratio test p value			0.100	0.157
Asthma symptoms			Adjusted rate	Adjusted rate
			ratio (95%CI)^a	ratio (95%CI)^{b, e}
<i>Physical activity per week:</i>				
None	1,520 (55)	1,235 (45) ^c	1.00	
Light, ≤1 hour	1,029 (60)	687 (40) ^c	0.96 (0.89, 1.03)	
Light, > 1 hour	643 (59)	442 (41) ^c	0.90 (0.75, 1.08)	
Vigorous, ≤1 hour	2,634 (64)	1,503 (36) ^c	0.92 (0.86, 0.98) ^d	
Vigorous, > 1 hour	1,641 (65)	887 (35) ^c	0.99 (0.93, 1.08)	

Wald test p value

0.009^d

CI: Confidence Interval

a Each analysis adjusted for age, gender, RHINE III smoking, educational level and RHINE II current asthma in the current asthma analysis, and RHINE II report of asthma symptoms in the asthma symptom analysis.

b Adjusted for the previous factors and RHINE III BMI as a categorical variable.

c Present, n (%): indicates one or more asthma symptoms present.

d $p < 0.05$

e No adjustment for BMI in the presence of the interaction.

Figure 1. RHINE III-all center cross-sectional study: interaction between physical activity and BMI categories^a with the outcome of asthma symptoms.

a BMI<20 not included in the graph due to low numbers of participants in this group.

b $p<0.05$ between those with a BMI of 20 to 24.99 compared to those with a BMI 25 to 29.99 at the given levels of physical activity.

DISCUSSION

In this study of middle aged adults, increasing frequency of lighter physical activity, but not vigorous activity, was a predictor of less current asthma (wheeze without cold, asthma attacks / asthma medications) over ten years. These associations were attenuated after BMI adjustment and no longer statistically significant. We could identify no association between physical activity and incident asthma over ten years. In the all centre cross-sectional study there was no association between physical activity and current asthma however there was an interaction between physical activity and BMI; indicating that those with normal BMI experienced a reduction in asthma symptoms associated with physical activity while those with a higher BMI did not.

The positive effect from physical activity on current asthma was attenuated by BMI adjustment in this study. This may indicate that BMI is a confounder in the association or that BMI may be a mediator of the association. Support for BMI as a mediator can be found in the biological explanations of the associations between physical activity and BMI (22-25) and also in RCTs demonstrating that physical activity can alter asthma outcomes (4, 5). Concomitantly, a number of pathophysiological mechanisms of how physical activity effects asthma, with and without BMI mediation, have been suggested. Physical activity has been found to improve insulin sensitivity (26) and that hyperinsulinemia may stimulate asthma through increasing Type 2 helper T cell responses and airway hyperresponsiveness (27). Considering possible BMI mediation, the adipose tissue secreted adipokines (leptin and adiponectin) may influence insulin sensitivity (28) and potentially asthma (22). Other possible obesity-asthma mechanisms are the effect of weight on lung mechanics, gastro-oesophageal reflux and obstructive sleep apnoea (29). Overall, there are plausible pathways through which physical activity may influence asthma as

an independent factor or through BMI mediation; however it should not be discounted that the physical activity and asthma associations may be due to BMI confounding.

An intriguing finding seen in the longitudinal study was the positive effect on current asthma from lighter activity but a trend towards a negative effect from vigorous activity. An increased risk of asthma from vigorous activity has been reported in cross sectional studies (30-32) and studies of athletes (33-36) previously. The trend towards an increased risk with vigorous activity observed may be due to exercise induced asthma or that RHINE was undertaken in Scandinavia, so a possible effect from exercising in dry cold air, as per winter sports, people may increase the risk of airway hyper-responsiveness and asthma symptom development (36, 37). However without further information about the type of exercise (i.e. endurance /resistance or indoor/outdoor) it is difficult to speculate as to the cause of the trend.

In the all centre cross-sectional study an interaction demonstrated that more physical activity was associated with reduced asthma symptoms in normal BMI participants but not overweight participants. It is important to remember that as a cross-sectional analysis this result could be interpreted as overweight people with asthma symptoms being less likely to be physically active, and a previous study of adolescents concluded this from similar results (38). Without knowing the temporal relationship, the direction of the association can only be speculated at.

No significant effect of physical activity on asthma incidence was found. Some previous studies have also found no association (10, 11) whilst other studies have found an effect (7, 39). A common factor in the studies finding an association was no mention of confounding adjustment. In our analysis a limitation was low statistical power. Overall more research is required to discern trends.

The strengths of this study are its long-term follow-up and comparison across study designs. A weakness is that physical activity was self-reported and as such prone to overestimation by participants (40). This is likely to result in the underestimation of the associations observed. Additionally the light and vigorous physical activity questions make it difficult to discern the effect from moderate physical activity or consider the duration and type of activity. The asthma outcomes were also self-reported and hence there is a risk that other morbidity may present with similar symptoms; this may amplify the association observed if physical activity is protective for these conditions. A further weakness is possible reverse causality, with previous levels of asthma (e.g. childhood asthma) and obesity potentially influencing physical activity. To address this we undertook a sensitivity analysis with adjustment for RHINE I asthma and BMI and found no change in associations. Loss to follow up is a potential consideration however there was no interaction between the RHINE II factors and loss. It also should be noted that the association between physical activity and asthma may be different in this European population where physical activity may be prevalent and average BMI lower than, for example, North America (41).

Current Global Initiative for Asthma guidelines state that there is no evidence that physical activity has an effect on asthma, but encourages people with asthma to be physically active for a general health benefit (42). This research indicates that physical activity over the longer term may have an effect on asthma and that there may be an absence of increased benefit from increased physical activity intensity. Additionally, this study highlights the potential complex nature of the association between physical activity, BMI and asthma. It may be that physical activity is only effective in reducing asthma symptoms in people with a normal BMI; however other large studies will be required to explore this.

Conclusion

In this study lighter physical activity was found to reduce current asthma in middle aged adults over time, whilst benefit from increasing intensity of physical activity was not evident over time. After adjustment for BMI the association was no longer significant. Cross-sectionally at different levels of BMI, the association between physical activity and asthma differed. These results indicate the complex association between physical activity, BMI and asthma, with the possibility that the benefit from physical activity may differ according to BMI.

This article has an online data supplement, which is accessible from this issue's table of content online at XXXX.

Declaration of interest: none.

Acknowledgements The authors thank the RHINE staff and study participants.

Contributors Conception and design: MR, CJ, FR, AJ, MW, BB, MH, EL, VS, CS, SD;

Analysis and interpretation: MR, CJ, CS, SD; Drafting the manuscript for important intellectual content: MR, CJ, FR, AJ, MW, BB, MH, EL, VS, WR, CS, SD; Final approval of the version to be published: MR, CJ, FR, AJ, MW, BB, MH, EL, VS, WR, CS, SD.

Funding

RHINE was supported financially by the Norwegian Research Council (Grant No. 214123), the Bergen Medical Research Foundation, the Western Norwegian Regional Health Authorities (Grant No. 911 892 and 911 631), the Norwegian Labour Inspection, the Norwegian Asthma and Allergy Association, The Faculty of Health of Aarhus University (Project No. 240008), The Wood Dust Foundation (Project No. 444508795), The Danish Lung Association, the Swedish Heart and Lung Foundation, the Vårdal Foundation for Health Care Science and Allergy Research, the Swedish Council for Working Life and Social Research, the Bror Hjerpstedt Foundation, the Swedish Asthma and Allergy Association, the Icelandic Research Council, and the Estonian Science Foundation (Grant No. 4350). S Dharmage is supported by an NHMRC.

REFERENCES

1. Nocon M, Hiemann T, Mueller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2008;15(3):239-46.
2. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Does regular physical activity reduce lung function decline and COPD risk among smokers? *Am J Resp Crit Care*. 2007;176(3):314-5.
3. Smidt N, de Vet HCW, Bouter LM, Dekker J, Exercise Therapy G. Effectiveness of exercise therapy: A best-evidence summary of systematic reviews. *Australian Journal of Physiotherapy*. 2005;51(2):71-85.
4. Heikkinen SAM, Quansah R, Jaakkola JJK, Jaakkola MS. Effects of regular exercise on adult asthma. *European Journal of Epidemiology*. 2012;27(6):397-407.

5. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. The Cochrane database of systematic reviews. 2013;9:CD001116.
6. Huovinen E, Kaprio J, Koskenvuo M. Factors associated to lifestyle and risk of adult onset asthma. *Respiratory Medicine*. 2003;97(3):273-80.
7. Lucke J, Waters B, Hockey R, Spallek M, Gibson R, Byles J, et al. Trends in women's risk factors and chronic conditions: findings from the Australian Longitudinal Study on Women's Health. *Women's health (London, England)*. 2007;3(4):423-32.
8. Garcia-Aymerich J, Varraso R, Anto JM, Camargo CA. Prospective Study of Physical Activity and Risk of Asthma Exacerbations in Older Women. *Am J Resp Crit Care*. 2009;179(11):999-1003.
9. Shaaban R, Leynaert B, Soussan D, Anto JM, Chinn S, de Marco R, et al. Physical activity and bronchial hyperresponsiveness: European Community Respiratory Health Survey II. *Thorax*. 2007;62(5):403-10.
10. Benet M, Varraso R, Kauffmann F, Romieu I, Anto JM, Clavel-Chapelon F, et al. The effects of regular physical activity on adult-onset asthma incidence in women. *Respiratory Medicine*. 2011;105(7):1104-7.
11. Beckett WS, Jacobs DR, Yu XH, Iribarren C, Williams D. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Resp Crit Care*. 2001;164(11):2045-50.
12. Eijkemans M, Mommers M, Draaisma JMT, Thijs C, Prins MH. Physical Activity and Asthma: A Systematic Review and Meta-Analysis. *Plos One*. 2012;7(12).
13. Johannessen A, Verlato G, Benediktsdottir B, Forsberg B, Franklin K, Gislason T, et al. Longterm follow-up in European respiratory health studies - patterns and implications. *Bmc Pulmonary Medicine*. 2014;14.

14. Kurtze N, Rangul V, Hustvedt BE, Flanders WD. Reliability and validity of self-reported physical activity in the Nord-Trondelag Health Study - HUNT 1. *Scandinavian Journal of Public Health*. 2008;36(1):52-61.
15. Gislason T, Bertelsen RJ, Real FG, Sigsgaard T, Franklin KA, Lindberg E, et al. Self-reported exposure to traffic pollution in relation to daytime sleepiness and habitual snoring: a questionnaire study in seven North-European cities. *Sleep Med*. 2016;24:93-9.
16. Holmen H, Wahl A, Torbjørnsen A, Jenum AK, Smastuen MC, Ribu L. Stages of change for physical activity and dietary habits in persons with type 2 diabetes included in a mobile health intervention: the Norwegian study in RENEWING HEALTH. *BMJ Open Diabetes Res Care*. 2016;4(1):e000193.
17. Ellekjaer H, Holmen J, Ellekjaer E, Vatten L. Physical activity and stroke mortality in women. Ten-year follow-up of the Nord-Trondelag health survey, 1984-1986. *Stroke*. 2000;31(1):14-8.
18. Woodhouse A, Pape K, Romundstad PR, Vasseljen O. Health care contact following a new incident neck or low back pain episode in the general population; the HUNT study. *BMC Health Serv Res*. 2016;16:81.
19. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). *European Respiratory Journal*. 1996;9:687-95.
20. Pekkanen J, Sunyer J, Anto JM, Burney P, Ecrhs. Operational definitions of asthma in studies on its aetiology. *European Respiratory Journal*. 2005;26(1):28-35.
21. Lee AH, Wang K, Scott JA, Yau KKW, McLachlan GJ. Multi-level zero-inflated Poisson regression modelling of correlated count data with excess zeros. *Statistical Methods in Medical Research*. 2006;15(1):47-61.

22. Kim SH, Sutherland ER, Gelfand EW. Is there a link between obesity and asthma? *Allergy Asthma Immunol Res.* 2014;6(3):189-95.
23. Thompson D, Karpe F, Lafontan M, Frayn K. Physical activity and exercise in the regulation of human adipose tissue physiology. *Physiol Rev.* 2012;92(1):157-91.
24. Conn VS, Hafdahl A, Phillips LJ, Ruppar TM, Chase JA. Impact of physical activity interventions on anthropometric outcomes: systematic review and meta-analysis. *J Prim Prev.* 2014;35(4):203-15.
25. Brashier B, Salvi S. Obesity and asthma: physiological perspective. *J Allergy (Cairo).* 2013;2013:198068.
26. Balkau B, Mhamdi L, Oppert JM, Nolan J, Golay A, Porcellati F, et al. Physical activity and insulin sensitivity: the RISC study. *Diabetes.* 2008;57(10):2613-8.
27. Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy (Cairo).* 2013;2013:627384.
28. Yadav A, Kataria MA, Saini V, Yadav A. Role of leptin and adiponectin in insulin resistance. *Clinica Chimica Acta.* 2013;417:80-4.
29. Novosad S, Khan S, Wolfe B, Khan A. Role of obesity in asthma control, the obesity-asthma phenotype. *J Allergy (Cairo).* 2013;2013:538642.
30. Jerning C, Martinander E, Bjerg A, Ekerljung L, Franklin KA, Jarvholm B, et al. Asthma and physical activity - A population based study results from the Swedish GA(2)LEN survey. *Respiratory Medicine.* 2013;107(11):1651-8.
31. Verlaet A, Moreira A, Sa-Sousa A, Barros R, Santos R, Moreira P, et al. Physical activity in adults with controlled and uncontrolled asthma as compared to healthy adults: a cross-sectional study. *Clin Transl Allergy.* 2013;3(1):1.

32. Uddenfeldt M, Janson C, Lampa E, Leander M, Norback D, Larsson L, et al. High BMI is related to higher incidence of asthma, while a fish and fruit diet is related to a lower-Results from a long-term follow-up study of three age groups in Sweden. *Respiratory Medicine*. 2010;104(7):972-80.
33. Helenius IJ, Tikkanen HO, Sarna S, Haahtela T. Asthma and increased bronchial responsiveness in elite athletes: Atopy and sport event as risk factors. *Journal of Allergy and Clinical Immunology*. 1998;101(5):646-52.
34. Bonini M, Gramiccioni C, Fioretti D, Ruckert B, Rinaldi M, Akdis C, et al. Asthma, allergy and the Olympics: a 12-year survey in elite athletes. *Current Opinion in Allergy and Clinical Immunology*. 2015;15(2):184-92.
35. Carlsen KH, Anderson SD, Bjermer L, Bonini S, Brusasco V, Canonica W, et al. Exercise-induced asthma, respiratory and allergic disorders in elite athletes: epidemiology, mechanisms and diagnosis: Part I of the report from the Joint Task Force of the European Respiratory Society (ERS) and the European Academy of Allergy and Clinical Immunology (EAACI) in cooperation with GA(2)LEN. *Allergy*. 2008;63(4):387-403.
36. Langdeau JB, Turcotte H, Bowie DM, Jobin J, Desgagne P, Boulet LP. Airway hyperresponsiveness in elite athletes. *Am J Resp Crit Care*. 2000;161(5):1479-84.
37. Kippelen P, Anderson SD. Pathogenesis of Exercise-Induced Bronchoconstriction. *Immunology and allergy clinics of North America*. 2013;33(3):299-+.
38. Lawson JA, Rennie DC, Dosman JA, Cammer AL, Senthilselvan A. Obesity, diet, and activity in relation to asthma and wheeze among rural dwelling children and adolescents. *J Obes*. 2013;2013:315096.
39. Thomsen SF, Ulrik CS, Kyvik KO, Larsen K, Skadhauge LR, Steffensen IE, et al. Risk factors for asthma in young adults: a co-twin control study. *Allergy*. 2006;61(2):229-33.

40. Helmerhorst HJF, Brage S, Warren J, Besson H, Ekelund U. A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *International Journal of Behavioral Nutrition and Physical Activity*. 2012;9.
41. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet*. 2012;380(9838):247-57.
42. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2015. Available from: www.ginasthma.org.

