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Does physical activity strengthen lungs and protect against asthma in childhood? A systematic review

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Each of the listed authors (RC, EM, JK, SD, MR, FP) contributed to the conception and design, acquisition of data, or analysis and interpretation of data. RC produced the first draft, and all other authors (EM, JK, SD, MR, FP) edited and revised it critically for important intellectual content. All authors (RC, EM, JK, SD, MR, FP) reviewed and approved the final version of the manuscript and accept accountability for the manuscript.

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ABSTRACT

BACKGROUND: Physical activity may be a potentially modifiable risk factor for asthma and driver of lung function development. This systematic review aimed to summarise the available evidence concerning the longitudinal effect of physical activity on the development of asthma, the persistence of asthma symptoms, and lung function outcomes in children and adolescents.

METHODS: PubMed and EMBASE electronic databases were searched for all original articles that investigated the longitudinal association between physical activity and asthma outcomes or lung function outcomes in children and adolescents. The search and data extraction were conducted by two independent researchers. Methodological quality of the included studies was assessed using two critical assessment tools.

RESULTS: The literature search retrieved 2298 publications from the electronic databases. All articles were screened and 2289 were subsequently excluded, resulting in nine longitudinal studies eligible for inclusion in this review. Two studies found no association with incident wheeze, and two of four found no association with various asthma outcomes. Three studies investigated the effect on lung function, with one finding an association in boys only, one in girls only and one found no associations.

CONCLUSION: The evidence was highly inconsistent for both the relationship between physical activity and asthma and lung function outcomes. Hence, we conclude that there is insufficient evidence to suggest that physical activity has a long-term effect on the risk of asthma development

in youth. Furthermore, there is insufficient evidence to determine the longitudinal effects of physical activity on lung function in children.

KEYWORDS: adolescents, asthma, children, lung function, physical activity, systematic review

INTRODUCTION

Asthma affects approximately 339 million people worldwide(1), and is the most common chronic condition affecting children. It is characterised as chronic inflammation of the airways(2) associated with reversible airway obstruction and bronchial hyperresponsiveness(3) leading to symptoms of coughing, wheezing and shortness of breath. Additionally, lung function (LF) impairment in childhood leads to abnormal patterns of LF growth and decline in adulthood(4).

Recent efforts have focused on identifying potentially modifiable targets for asthma prevention(3, 5). One such factor is physical activity (PA); which is thought to potentially play a protective role against asthma through its known anti-inflammatory effects(6). For this reason, several international health authorities, including the World Health Organisation (WHO), endorse PA participation for variety of health benefits(7-9). Currently, a minimum of 60 minutes of moderate to vigorous physical activity per day is recommended for children and adolescents between the ages of 5 and 17 years(7-9). However in 2010, the WHO estimated that globally 81% of adolescents aged between 11 and 17 years were insufficiently active(10, 11).

Two systematic reviews investigating the effects of PA on asthma incidence and prevalence have previously been published(12, 13). However, the first review was published seven years ago, and did not restrict to child populations(13). The second, more recent review seemed to have overlooked several cohort studies(14-19) including all of those included in the present review, and furthermore, did not consider the effect of PA on asthma symptoms(12). Neither review restricted their inclusion to cohort designs, nor did they investigate the effect of PA on LF in children(12, 13).

The present review, therefore, intends to collate the literature regarding the longitudinal effect of PA on asthma incidence, the persistence of asthma symptoms, and on LF outcomes, focussing specifically on youth. This review will also be the first to synthesise the available evidence on the relationship between PA and LF outcomes in youth. Specifically, this systematic review aims to address the following research questions:

1. Do children and adolescents who engage in increased PA experience (a) decreased risk of developing asthma or (b) reduced asthma symptoms among asthmatics, compared to their less active peers?

2. Are higher levels of PA associated with increased LF in children and adolescents (a) with asthma, and (b) without asthma?

METHODS

This systematic review was registered with Prospero, the international prospective register of systematic reviews (registration number: CRD42018098833) and the reporting of this review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines(20).

Search Strategy:

A systematic search was conducted for publications in the PubMed and EMBASE electronic databases to obtain all articles that investigated the relationship between PA and asthma or lung function. Key terms were identified for each construct and combined using the Boolean operators "OR" within the construct and "AND" between constructs. Medical Subject (MeSH) terms were included in the PubMed Search as appropriate. The complete search strategies are appended below (Appendix 1). Furthermore, reference lists were manually checked to identify any articles that may have been missed by the search. The search was conducted independently by two researchers (RC and FMP) and any discrepancies were resolved by a third (MAR). A final search was conducted on 18th March 2019.

Eligibility Criteria:

Studies where PA was measured as the exposure variable and asthma status or LF were measured subsequently in children and adolescents up to the age of 18 years were included in this review. Cross sectional, case control studies and intervention studies in which children underwent exercise programmes or fitness training were excluded, as this review was primarily interested in the longitudinal effect of habitual PA. Studies where sedentary behaviour was the exposure of interest were excluded, since PA and sedentary behaviour are considered to be distinct behaviours(21). Additionally, animal and *in vitro* studies, and those conducted in special populations (e.g. athletes), non-English language articles, conference abstracts and letters or reviews that did not present original data were excluded. There were no restrictions on date of publication. Inclusion and

exclusion criteria were assessed independently by two researchers (RC and FMP) and any discrepancies were resolved by a third (MR).

Data Extraction:

The following information was extracted from each eligible article: author, date of publication, location of study, the study population, study design, measurement tools and timing of exposure and outcome measurements, all confounding variables that were adjusted for in the analysis, unadjusted and adjusted (where both were available) reported measures of association, and the author's conclusions. In an attempt to include all eligible articles, one author was contacted, and clarification of the results of their paper was obtained(22). Data were tabulated separately according to the outcome measured.

Critical Appraisal:

The quality of eligible articles was assessed using two critical appraisal tools. First, articles were assessed using the preliminary version of the Risk Of Bias In Non-randomized Studies - of Exposures (ROBINS-E; available online at http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-e/). This tool assessed bias in several aspects of a study: Bias due to confounding, participant selection, exposure classification, departures from intended exposure, missing data, outcome measurement and selection of the reported result. Each study was then given an overall bias score. In addition, articles were assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Each article was awarded a score out of four for selection bias, two for comparability and three for bias in the outcome assessment, with a maximum total score of nine points. An *a priori* decision was taken to exclude articles that scored poorly (defined as an overall NOS score less than 5 and an overall ROBINS-E score greater than moderate) on both tools.

RESULTS

Literature Search:

The search identified a total of 2298 articles. Of these, 739 duplicates were removed, and a further 1496 were excluded after screening of titles and abstracts. The remaining 63 articles were assessed in detail, and 53 publications were subsequently excluded as they did not meet the inclusion criteria (Figure 1). Finally, the paper by Twisk *et al*. was excluded as the longitudinal analysis included

outcomes measured beyond the age of 18 years(22). The process resulted in nine articles eligible for inclusion in this review. Included studies were stratified by outcome (Tables 1 and 2).

Critical appraisal:

Using the ROBINS-E tool, included studies were found to contain low(14, 17, 18, 23) to moderate(15, 16, 19, 24, 25) levels of overall bias. Additionally, studies scored five(16), six(15, 19, 26), seven(14, 18, 23) or eight(17, 24) out of nine points on the NOS, indicating moderate to high quality; hence all studies were included in this review. Individual quality assessment scores are presented in table 3.

PA and Asthma Outcomes:

Six studies assessed the relationship between PA and asthma-related outcomes(14-19) (table 1). All of these studies were conducted in high-income countries, namely Norway(17), the Netherlands(18, 19), Germany(14), USA(16) and Canada(15). All studies adjusted for one or more potential covariates; importantly, five of the six studies adjusted for sex(14, 16-19) and three adjusted for body mass index (BMI)(14, 16, 19). Four studies accounted for socioeconomic status (SES), or parental or caregiver education(14-16, 18).

i. General population studies

Two studies included children with and without asthma at baseline(15, 17). Protudjer *et al* analysed data from 489 children who were 8-9 years old at baseline and followed up at 12-14 years of age(15). Although their study was conducted in a birth cohort, Byberg *et al*. analysed data from 617 children who were asked about their PA between the ages of 3-6 and 6-10 years at the first follow up (when girls were 10.8 years and boys were 11.8 years old). Asthma outcomes were assessed at a second follow up when children of both sexes were aged 12.8 years(17).

Protudjer *et al.* employed a paediatric allergist to ascertain asthma status(15), while in the Byberg study, maternal-reports of ever or current asthma, wheeze and shortness of breath were assessed using the ISAAC questionnaire(17).

PA data was measured subjectively via parental-reports in both studies. Based on the Stanford Brief Activity Survey, Byberg *et al.* asked parents to recall their child's activity levels when they were 3-6 years of age(17). Protudjer *et al*. assessed frequency of PA from a close-ended response to the question: "In the last 12 months, how many times a week does your child engage in vigorous or competitive PA long enough to make him/her breathe hard?"(15).

The two studies produced inconsistent results. Protudjer *et al*. found no association between low levels of PA at age 9 years and paediatric allergist-defined asthma at age 13(15), while Byberg *et al.*

found low levels of PA between the ages of 3 and 6 years to be positively associated with ever asthma at age 10.8 in girls and at age 11.8 in boys(17).

ii. Asthma-free population studies

Participants were free of asthma or wheeze at baseline in two of the six studies(14, 18). The study populations consisted of 347 young children(18) and 2910 adolescents(14), respectively. Driessen and colleagues were the one team to investigate this relationship in early life, measuring PA by accelerometery at age 2 years and measuring wheeze at 4 years of age(18). In contrast, the large German study by Vogelberg *et al*. followed children for approximately 6 years from the baseline PA measurement at 9-11 years, until the adolescents were 15-17 years old(14).

Driessen *et al*. used the ISAAC questionnaire to measure ever or current asthma, wheeze and shortness of breath based on parental report(18), while Vogelberg *et al*. used their own study questionnaire to identify their primary outcome - incident wheeze(14). Similarly, Vogelberg *et al.* used their own study questionnaire to collect PA data(14), while Driessen *et al.* employed accelerometery(18).

Driessen *et al*. found that PA measured by accelerometery in the second year of life was not associated with wheeze at ages 3 and 4 years(18). In their unadjusted analysis, Vogelberg found that increasing PA was significantly associated with decreasing prevalence of wheeze in older adolescents(14), however, when they adjusted for active smoking, the association was no longer observed.

iii. Asthma population studies

Two studies were conducted in children with asthma(16, 19). These studies analysed 147 children aged 5-12 years(16) and 260 adolescents aged 10-14 years(19) at baseline. In their study, Nnodum *et al*. collected data on asthma symptoms using a Paediatric Asthma Diary (PAD) completed twice daily by child and parent/caregiver for a period of 3 to 6 months(16). The PAD assessed a number of daytime and night-time symptoms on 6- and 4- point Likert scales, respectively(16). In contrast, Tiggelman *et al.* used the Asthma Control Questionnaire to measure asthma control with a follow up period of one year(19).

In both studies, PA data was collected subjectively via self-report(16, 19). Nnodum *et al.* used the Physical Activity Questionnaire for Children (PAQ-C)(16) while Tiggelman *et al.* did not specify which questionnaire was used(19).

The studies reported inconsistent results. Nnodum *et al*. concluded that more PA was longitudinally associated with more reported asthma symptoms(16), while Tiggelman *et al*. concluded that habitual PA was not longitudinally associated with asthma control(19).

PA and LF Outcomes:

Three of the nine eligible studies used spirometry to collect forced expiratory volume (FEV) and forced vital capacity (FVC) as outcome data(23, 24, 26) (table 2). All three studies adjusted for BMI, height, maternal education and parental smoking. Only Ji *et al*. adjusted for earlier LF indices in their longitudinal data analyses(24). All studies presented results stratified by sex(23, 24, 26). No studies were found that investigated the association in children with asthma.

i. General population studies

Two large Brazilian studies analysed data from the same birth cohort whose participants were followed up and spirometric measurements collected at the ages of 11, 15 and 18 years(23, 26). The earlier study by Menezes *et al* examined the relationship between the change in leisure-time PA status between the ages of 11 and 15 and LF parameters measured at age 15(26), while the more recent study by da Silva and colleagues in 2016 used PA exposure data at age 11 and 15 and spirometry outcome data from the cohort at 15 and 18 years(23).

Both analyses collected information on PA through self-report questionnaires, but neither specified which PA questionnaire was used. In addition, PA was categorised using different thresholds. Menezes *et al*. defined being active as 300 minutes of PA per week(26), while da Silva *et al*. categorised being active as either 150 minutes of moderate PA or 75 minutes of vigorous-intensity PA per week(23).

Both studies measured FEV_1 and FVC, although their aims differed. In their study, da Silva *et al* focussed on gains in pulmonary function from age 15 to 18 years(23) while Menezes *et al* aimed to assess the effect of change in PA on LF at 15 years(26). Results were stratified by gender.

Reported results were highly inconsistent. Da Silva *et al*. found PA at 11 and 15 years to be longitudinally associated with larger gains in FEV_1 and FVC between the ages of 15 and 18 in boys(23). The authors noted that boys who became active from age 11 to age 15 did not benefit from the increased gains in pulmonary function, hence they emphasised the importance of PA in early adolescence. No significant associations between PA and pulmonary function gain in girls were observed. In contrast, Menezes *et al* found that girls who were physically active during their leisure time at age 11 and 15 years had higher percent predicted FVC (3.573 [1.015, 6.130], p = 0.006) at age 15 years compared to girls who were inactive in their leisure time at both ages. There were no

significant associations with FEV_1 in girls, and no associations were found in boys. The authors did not observe any associations between total PA - as opposed to leisure time PA - and LF.

ii. Asthma-free population studies

One study excluded children with asthma at baseline. The large Chinese study analysed data from 1713 asthma- free children aged between 9 and 11 years and followed them up for 18 months(24).

PA data were collected through self-report questionnaires with the "guidance of trained investigators", but the authors did not state which PA questionnaire was used. Children were considered physically active if they participated in at least 30 minutes of sport and/or vigorous free play at least 3 times per week.

Ji and colleagues investigated the effect of PA on LF growth and found no statistically significant associations with FEV_1 and FVC in either boys or girls(24). The mean [standard error] FEV_1 and FVC values for boys who were active at one or both surveys were 0.24 [0.01] and 0.29 [0.01], respectively, compared to FEV_1 and FVC values of 0.25 [0.01] and 0.29 [0.01] in boys who were inactive at both time points. Similarly, the mean [standard error] growth in FEV_1 and FVC girls who were active at one or both time points were 0.27 [0.01] and 0.28[0.01] respectively, compared to 0.25 [0.01] and 0.27 [0.01] for girls who were inactive at both timepoints(24).

DISCUSSION

Summary:

The present systematic review attempted to determine the longitudinal effect of PA on the development of asthma and the persistence of asthma symptoms in youth. It is also the first to review the evidence of the relationship between PA and subsequent LF outcomes.

The results of these studies were highly inconsistent and did not produce any clear evidence for the effects of PA. Briefly, two studies reported a positive association between low levels of PA and asthma symptoms(16), and ever asthma(17). No associations were observed between PA and incident wheeze in two studies(14, 18) nor with asthma control(19), nor with paediatric allergist-defined asthma(15). Of the three LF studies, one observed an association in girls only(25), one in boys only(23) and one found no associations in either boys or girls(24). The differential results for effect on LF by sex may be due to the ages at which measurements were taken, since girls experience growth-related changes at earlier ages compared to boys, who experience a period of

246 rapid growth between the ages of 15 and 18 years(23, 27). This is consistent with the findings of the
247 studies, where the study that measured LF outcomes at 15 found an association in girls only(25),
248 while when LF was measured at 18 years an association was observed in boys only(23). Additionally,
249 no associations were found in pre-adolescent children(24), who had not yet experienced growth-
250 related changes. Despite the inability to meta-analyse results, it is apparent that most studies found
251 little evidence of relationship between PA and various respiratory outcomes.

252 Interestingly, a recent publication that found that increases in aerobic fitness during childhood and
253 adolescence were longitudinally associated with higher lung function parameters(28). Whilst this
254 study differs from the present one in that the exposure investigated was fitness measured using
255 cycle ergometer tests rather than habitual physical activity, the positive finding reported by Hancox
256 and Rasmussen adds another dimension to the complexity of the evidence(28). There were some
257 similarities in their reported results, compared to the studies contained within this review.
258 Specifically, in their article, Hancox and Rasmussen reported associations with FEV1 and FVC, but not
259 FEV1/FVC ratio, which they propose indicates an association with lung size rather than an
260 association with the quality of the airways(28). They further stated that their associations were
261 stronger in boys, which again may be due to the older developmental age of participants at time of
262 measurement(28).

263 The present findings are discordant with those of the two existing systematic reviews, which found
264 PA to play a protective role against the incidence of asthma in both adults and children(12, 13). This
265 is likely due to important differences between those reviews and the present one. Firstly, the
266 Eijkemans review did not restrict by population age nor study design(13). Due to the nature of their
267 design, longitudinal studies provide stronger evidence for temporality than cross-sectional studies,
268 hence the present review restricted to cohort studies. In their meta-analysis of five longitudinal
269 studies (I^2= 45%), Eijkemans *et al.* concluded that higher levels of PA were associated with lower
270 incidence of asthma (odds ratio 0.88 (95% CI: 0.77–1.01)(13). However, all of the studies conducted
271 in children were cross-sectional in nature, hence they did not have the longitudinal evidence to
272 support this conclusion in child populations(13). On the other hand, the Lochte *et al*. review did
273 restrict their population age but did not restrict to longitudinal study design(12). Although the I^2
274 values obtained were moderate (60.6% for both fixed and random effects) the articles included in
275 the meta-analysis had varying definitions of PA(12). For example, one study measured television
276 viewing time(29), and this was included as a proxy measure for low levels of PA despite some
277 research suggesting that there is a distinction between low PA and sedentary behaviours(30, 31). As
278 a result, the articles included in the Lochte *et al*. review did not correspond with those contained
279 within the present review, since the present review elected to exclude sedentary behaviours(12).

The true relationship between PA and subsequent asthma or LF may still be masked by several analytical issues. First, the definitions and categorisations of PA used varied greatly between the included studies; an issue not unique to this paper. There remains a critical lack of standardised protocols for the measurement, processing and categorisation of PA within the scientific community. This presents an important barrier against comparing and collating PA studies. Future studies will need to address these challenges in order to improve the generalisability of PA research. Furthermore, the included studies adjusted for a variety of potentially confounding variables. Although most accounted for sex through either adjustment or stratification, many, including one of the studies that reported a positive association, did not adjust for other potentially important factors such as BMI, SES, passive smoking or ethnicity. Overall, however, there was no consistency between the variables included for adjustment and the associations found. Future studies should include participants who are asthma-free at baseline to investigate whether PA affects asthma development and LF growth, and participants with varying asthma severity, to assess the impact of PA on asthma symptoms and control and LF growth. When designing and conducting further research in this area, it may also be beneficial to consider the length of follow up time required to observe an effect. For example, when measuring the effect on lung function or asthma incidence, it is necessary to study the effect over multiple years.

Strengths:

This review was systematically and thoroughly conducted by two independent researchers in order to identify and include all relevant data on this topic. Searches were performed in two distinct databases and included a manual search of reference lists in order to ensure that relevant articles were not overlooked. Furthermore, the quality assessment of included articles was conducted using two critical appraisal tools – the ROBINS-E and the NOS, the results of which appeared to be largely congruous for each included article. Finally, the included articles were of moderate to high quality.

Limitations:

In contrast, this review had several limitations. Firstly, substantial variation in the methodologies of the included studies prevented the intended meta-analysis of the data. The included studies varied greatly not only in the outcomes measured, but also in their specific exposure and outcome measurement techniques, the thresholds and definitions used, the range of participant ages and duration of follow periods, and in the reporting of their results. Secondly, although critical appraisal of the studies was conducted, the review is limited by the critical appraisal tools available. The NOS Scale has drawn some criticism for its potential to produce arbitrary results(32). Similarly, the more detailed ROBINS-E tool has been criticised for being time-consuming, confusing, and for failing to

assess some sources of bias(33). Additionally, the small number of included studies meant that further analyses to investigate effect potential modification by factors such as age bracket and asthma status, could not be performed.

Conclusions:

In conclusion, due to the highly inconsistent results of the included studies, this systematic review has found that there is insufficient evidence to determine the longitudinal effect of PA on subsequent asthma and LF outcomes in children and adolescents. A robust tool for the measurement of PA in children and adolescents is lacking, as is a standardised analytical methodology. These issues must be circumvented for further longitudinal research to meaningfully assess these relationships.

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410 **TABLES**

411 Table 1: Details of six included articles that investigated the effect of physical activity on asthma outcomes.

Author, Date, Location	Sample Size and Participant Age	Physical Activity Measurement	Asthma Outcome Measurement	Main Effects	Covariates included	Author's Conclusions
General population studies						
Byberg, 2016 (17) Norway; "the Stavanger study"	617 children followed from birth. At first follow up girls were 10.8 years and boys were 11.8 years old. At the second follow up both sexes were aged 12.8 years.	Maternal reports of child's physical activity at age 3-6 and ages 6-10 years using the "Stanford Brief Activity Survey", a questionnaire validated for adults. Activity was categorised as low = passive and/or not so active, normal = active, high activity = very active.	Parental reports of doctor's diagnosis of asthma ever was evaluated at the first follow up. At the second follow up children responded to the ISAAC questionnaire and current asthma (defined as ever asthma and asthma symptoms or the use of asthma medications in the last 12 months) was evaluated.	a) Asthma ever by first follow-up: PA at 3-6 years n=454 (LR-p = 0.014); OR (95%CI) Normal PA n=275 (ref); Low PA n=57 3.61(1.56, 8.36) High PA n=122; 1.34(0.61, 2.97) PA at 6–10 years n=558 (LR-p =0.038); OR (95%CI) Normal PA n=351 (ref) Low PA n=92; OR=2.52(1.24, 5.12) High PA n=115; 1.02(0.46, 2.28) b) Current asthma at second follow-up: PA at 3-6 years n=361 (LR-p =0.475); OR (95%CI)	a) Asthma ever at first follow up: sex, gestational age, mother's preeclampsia and mother's asthma. b) Current asthma at second follow up: sex, mother's preeclampsia	Physical activity in early childhood is associated with asthma later in childhood.

				Normal PA n=220 (ref) Low PA n=48; OR=1.92(0.66, 5.59) High PA n=93; 1.40 (0.55, 3.55) PA at 6–10 years n=426 (LR-p =0.177) Normal PA n=274 (ref.) Low PA n=69; 1.98 (0.80, 4.85) High PA n=83; 1.97 (0.83, 4.67)	and mother's asthma.	
Protudjer, 2012 (15) Canada "1995 Manitoba Prospective Cohort Study"	489 children aged 8-9 (mean 8.6± 0.5) year olds at baseline followed up at 12-14 (mean 12.6± 0.5) years	Parental reports of physical activity and screen time through adapted questionnaire at 8-10 years. Physical activity was binary (active or inactive) to represent whether children were achieved ≥60 mins of activity daily. Screen time treated as binary outcome with a threshold of screen time above or below 1 hour daily.	Asthma status ascertained by paediatric allergist assessment at baseline and follow-up according to the Canadian Asthma Consensus Guidelines and based on semi-structured asthma history from children and parents and physical examination.	All participants: a) Asthma at 8–10 years; Model 1a 0.93 (0.76–1.15) p=0.50 Model 2b 0.91 (0.73–1.15) p=0.44; b) Asthma at 12–13 years Model 1a 1.07 (0.82–1.39) p=0.64; Model 2b 1.03 (0.78–1.37) p=0.83;	Model a) adjusted for region of residence and ethnicity. Model b) adjusted for region of residence, ethnicity, parental income, and education.	"Physical activity frequency was not associated with asthma… results fell short of demonstrating a prospective association between physical activity and asthma."
Asthma-free population studies						

Driessen, 2014 (18) The Netherlands; "The Generation R study"	347 children followed from birth. Mean ages at follow ups were 2, 3 and 4 years.	At age 2 years, an ActiGraph accelerometer worn for at least 400 mins on 2 days (1 weekend, 1 weekday). Epoch length=15s. Physical activity was categorised as light (302–614 counts/15 sec), moderate (615–1,230 counts/15 sec), or vigorous activity (≥1,231 counts/15 sec). Data were adjusted for accelerometer wear time by calculating the mean percentage of physical activity per day relative to the number of minutes per day of wearing the accelerometer.	Parental reports of wheeze and shortness of breath, assessed by the ISAAC questionnaire at 2, 3 and 4 years. Current wheeze and shortness of breath were defined as at least one episode of wheeze or shortness of breath in the third and fourth year, respectively. Data at age 2 were not used as an outcome.	a) Wheeze at age 3: Univariate Model OR (95%CI): LPA 0.97 (0.86–1.08) p=0,56; MVPA 1.01 (0.89–1.15) p=0.86; Multivariate Model OR (95%CI): LPA 0.94 (0.83–1.06) p=032, MVPA 1.00 (0.88–1.15), p=0,7. b) Wheeze at age 4 years: Univariate model OR (95% CI): LPA 0.99 (0.89–1.11) p=0.87; MVPA 1.01 (0.88–1.16) p=0.92; Multivariate model OR (95% CI): LPA 0.95 (0.84–1.08) p=0.43; MVPA 1.00 (0.85–1.18) p=0.96 c) Shortness of breath at age 3: Univariate model OR (95% CI) Multivariate model OR (95% CI): LPA 0.95 (0.85–1.06) p=0.35, MVPA 1.00 (0.88–1.13) p=0.96. d)Shortness of breath at age 4: Univariate model OR (95% CI): LPA 1.09 (0.96–1.22), p= 0.19; MVPA	Maternal BMI, maternal age, maternal educational level, household income, infant's consumption of vegetables and salty snacks in second year of life, infant's gender, day care attendance in second year of life and infant's motor function.	"Physical activity may not play an important role in the development of respiratory symptoms in pre-school children."

				1.09 (0.95–1.26) 0.23 Multivariate model OR (95% CI) LPA 1.04 (0.91–1.19), p=0,54, MVPA 1.08 (0.93–1.25), p=0.33.		
Vogelberg, 2007 (14) Germany; "Study on Occupational Allergy Risks (SOLAR)"	2910 children aged 9-11 years (wheeze-free) at baseline followed up at 15-17 years.	Leisure time activity assessed via questionnaire, categorised into 1) four categories of sport frequency between not more than once per month and 3 times per week; 2) computer work and TV watching ≥ 1hour per day; and 3) visiting a discotheque (yes or no).	Incident wheeze identified by questionnaire.	Adjusted OR for incident wheeze OR (95%CI): Sport >3 times per week versus ≤ once per month 0.8 (0.5–1.3); Computer work >1 h.day-1 versus≤1 h.day-1 1.1 (0.8–1.5); TV watching >1 h.day-1 versus ≤1 h day-1 1.1 (0.9–1.5); Visiting discotheques yes versus no 1.0 (0.8–1.3). When stratifying the analysis for smokers and non-smokers, no significant association was found between leisure time activity and wheeze.	SES, BMI, sex, passive and active smoking	A “significantly negative association was found between wheeze and increasing frequency of sport” in the crude analysis, but "The association between physical activity and new onset of wheeze disappeared

						when active smoking was taken into account."
Asthma populations						
Nnodum, 2017 (16) United States of America; "Asthma-DIET study"	147 children aged 5-12 years with physician-diagnosed asthma assessed daily for three 8-day periods. Followed up after 3 and 6 months.	Physical activity was self-reported at the end of each 8-day monitoring period using the Physical Activity Questionnaire for Children which has been validated for children.	Questionnaires assessed asthma medication use and asthma severity based on NAEPP guidelines, pre- and post- bronchodilator spirometry at baseline. Asthma symptoms assessed using the paediatric asthma diary, a validated questionnaire, completed twice daily for 8 days by child and their parent/caregiver during each of the monitoring periods.	Adjusted OR/RR (95%CI) Primary outcomes: a) Daytime asthma symptom diary scale 1.04 (1.00–1.09), p=0.04; b) Nocturnal asthma symptom diary scale 1.03 (1.00–1.06), p=0.01; c) Daily puffs of albuterol inhaler used 1.13 (0.81–1.58) p=0.4; d) Absent from school due to asthma 0.97 (0.54–1.74) p= 0.91; e) Doctor's visit due to asthma 1.09 (0.58–2.02) p= 0.79; f) Trouble breathing 1.05 (1.00–1.10) p=0.02; g) Bother due to asthma 1.04 (1.00–1.09) p= 0.04; h) Activity limitation due to asthma	Baseline age, gender, race, baseline BMI, caregiver's education, baseline asthma severity, inhaled corticosteroid use, and season	"Physically active children with asthma were more likely to report daytime asthma symptoms, nocturnal awakenings due to asthma, and being bothered by asthma symptoms."

				1.04 (1.00–1.09) p=0.06		

Tiggelman, 2014 (19) The Netherlands	260 adolescents with asthma aged 10-14 years at baseline, followed up after 1 year (T2) and 2 years (T3 - mean age 13.9 years). Only used data from T2 and T3.	Self-reported physical activity at T2. Activities were given a MET-score based on the Compendium of Physical Activities and MET-scores were then multiplied by the minutes that the adolescents spent on participating in these activities every week. These scores were combined to produce a total PA score.	ACQ at T2 and T3. The items were measured on a seven-point scale ranging from 0 (complete control) to 6 (very little control). Scores were then reversed, with higher scores on ACQ reflecting better asthma control. Lung function assessed by Spida5 to complement the ACQ but was not analysed separately.	Correlations between the model variables:
				a) Asthma control T2 and PA= -0.17;
				b) Asthma control T2 and PA= -0.13;
					BMI, gender and age	"Path analyses in the total group showed that habitual PA did not predict changes in psychosocial outcomes or asthma control over time."

Abbreviations: ISAAC – International Study of Asthma and Allergies in Childhood, PA – physical activity, LR – likelihood ratio, OR – odds ratio, LPA – light physical activity, MVPA – moderate-to-vigorous physical activity, BMI – body mass index, SES – socio-economic status, ACQ - Asthma Control Questionnaire, NAEPP – National Asthma Education and Prevention Program, MET – Metabolic Equivalent of Task

Table 2: Details of three included articles that investigated the effect of physical activity on lung functions outcomes.

Author, Date, Location	**Sample Size and**	**Physical Activity Measurement**	**Lung Function Outcome**	**Main Effect**	**Covariates included**	**Author's Conclusions**

	Participant		Measurement			
	Age					
General population studies						
da Silva, 2016 (23) Brazil; "1993 Pelotas Birth Cohort Study"	3571 children followed from birth. Mean ages at follow ups were 11, 15 and 18 years.	Physical activity was self-reported through questionnaires at ages 11 and 15 years. Classified based on the Compendium of Physical Activity where thresholds of 150 minutes of moderate physical activity and 75 minutes of vigorous-intensity physical activity per week were used to classify	Pre- and post-bronchodilator spirometry performed on all participants at ages 15 and 18 years. Pre-bronchodilator spirometry used for this study.	Boys FEV1 gain (z-score) Adjusted β (95% CI): Leisure-time PA: a) Never active: Ref; b) Active once: 0.095 (–0.009, 0.199); c)Always active: 0.177 (0.063, 0.290). Total PA: a) Never active: Ref; b) Active once: 0.057 (–0.062, 0.175); c) Always active: 0.137 (0.017, 0.258). FVC gain (z-score): Leisure-time PA: a) Never active: Ref; b) Active once: 0.072 (–0.011, 0.156); c) Always active: 0.146 (0.054, 0.237); Total PA: a) Never active: Ref b) Active once: 0.051 (–0.044, 0.147) c) Always active: 0.113 (0.016, 0.210).	Skin colour, family income at birth, maternal schooling at birth, birth weight, smoking during pregnancy, mother's height at birth, BMI at 11 years, BMI at 15 years, height at 15 years, wheezing in the previous year at 15 years, smoking at 15 years and Tanner stage at 15 years	Physical activity in early adolescence is associated with gains in pulmonary function by the end of adolescence in boys. No significant associations were found among girls.

		individuals as active or inactive.		Girls FEV1 gain (z-score) Adjusted β (95% CI): Leisure-time PA: a) Never active: Ref b) Active once: –0.006 (–0.064, 0.053) c) Always active: 0.030 (–0.079, 0.138) Total PA: Never active: Ref Active once: 0.044 (–0.016, 0.105) Always active: 0.018 (–0.063, 0.098) FVC gain (z-score): Leisure-time PA: Never active: Ref Active once: 0.015 (–0.045, 0.075) Always active: –0.054 (–0.164, 0.056) Total PA: Never active: Ref Active once: 0.020 (–0.041, 0.082) Always active: –0.005 (–0.087, 0.077)		
Menezes, 2012 (26)	4010 children followed since birth. Mean ages at follow	Physical activity was self-reported through questionnaires at	Pre- and post-bronchodilator spirometry performed at age	Boys Adjusted β (95% CI) FEV1: Changes of leisure-time PA (11–15yrs) Inactive–inactive: (ref)	Family income at birth, maternal schooling at birth, birth weight,	"Self-reported leisure-time physical activity was associated

Brazil; "1993 Pelotas Birth Cohort Study"	up were 11 and 15 years.	ages 11 and 15 years. Classified as active if they reached 300 minutes per week of physical activity. Change in physical activity were categorised as inactive–inactive (did not reach the 300 min/wk cut off point at age 11 or 15 years); inactive–active (reached the threshold at the age 15-year visit only); active–inactive (reached the threshold at	15 years.	Inactive–active: 0.204 (-1.339, 1.747) p-0.796 Active–inactive: -1.223 (-2.886, 0.439) p=0.149 Active–active: -0.912 (-2.436, 0.613) p=0.241 FVC: Inactive–inactive: (ref) Inactive–active: 1.269 (-0.381, 2.919) p=0.132 Active–inactive: -0.635 (-2.413, 1.142) p=0.484 Active–active: -0.395 (-2.025, 1.235) p=0.635 Girls Adjusted β (95% CI) FEV1: Changes of leisure-time PA (11–15yrs) Inactive–inactive: (ref) Inactive–active: 0.960 (-0.748, 2.669) p=0.270 Active–inactive: 0.704 (-0.823, 2.231) p=0.366 Active–active: 2.172 (-0.202, 4.546) p=0.073 FVC: Inactive–inactive: (ref) Inactive–active: 0.754 (-1.087, 2.595) p=0.422 Active–inactive: 0.435 (-1.210, 2.080)	smoking during pregnancy, mother's height at birth, height at 15 years, wheezing in past year, BMI, allergy status, and asthma medication.	with better effort-dependent lung function parameters, particularly among girls."

		the age 11-year visit only); or active–active (reached the threshold in both visits).		p=0.604 Active–active: 3.573 (1.015, 6.130) P=0.006		
Asthma-free population studies						
Ji, 2013 (24) China	1713 children aged 9-11 years followed up for 18 months.	Physical activity was self-reported through questionnaire in classroom with guidance of trained investigators. Classified as inactive or active, where active was defined as at least 30 mins of sport of vigorous activity 3 times a	Spirometry performed at baseline and at follow up.	FVC; Mean (SE) Difference Per Year in litres (dpy, l) Boys: Active (n=535): 0.29 (0.01) Inactive (n=323): 0.29 (0.01) Girls: Active (n=452): 0.28 (0.01) Inactive (n=403): 0.27 (0.01) FEV1; Mean (SE) Difference Per Year in litres (dpy, l) Boys: Active (n=535): 0.24 (0.01) Inactive (n=323): 0.25 (0.01) Girls: Active (n=452): 0.27 (0.01)	District, age, height, BMI, passive smoking, and maternal education.	"Physical activity is positively associated with lung function growth among Chinese school-aged girls." However, “the deficits in lung function growth for inactive girls were observed only in FEF but not FEV1 and FVC”.

	week.	Inactive (n=403): 0.25 (0.01)

Abbreviations: PA – physical activity, BMI – body mass index, FEV_1 – forced expiratory volume in one second, FVC – forced vital capacity, SE – standard error, DPY – difference per year, ref - reference

Table 3: The ROBINS-E and NOS quality assessment scores for each of the nine included studies.

	Newcastle-Ottawa Scale				Risk of bias in non-randomised studies – E (ROBINS-E)							
STUDY	**Selection**	**Comparability**	**Outcome**	**Total Score**	**Confounding**	**Participant selection**	**Exposure classification**	**Departures from intended exposure**	**Missing data**	**Outcome measurement**	**Selection of the reported result**	**Overall bias**
Byberg (2016) (17)	4	2	2	8/9	moderate	low	moderate	low	low	low	low	low
da Silva (2016) (23)	2	2	3	7/9	low	low	low	low	moderate	low	low	low
Driessen (2014) (18)	4	2	1	7/9	low	low	low	low	low	low	low	low
Ji (2013) (24)	3	2	3	8/9	moderate	moderate	moderate	low	low	low	low	moderate
Menezes (2012) (26)	2	2	2	6/9	low	low	low	low	moderate	low	low	moderate

Nnodum (2017) (16)	1	2	2	5/9	low	low	moderate	low	moderate	moderate	moderate	moderate
Protudjer (2012) (15)	2	1	3	6/9	moderate	moderate	moderate	low	low	low	low	moderate
Tiggelman (2014) (19)	2	2	2	6/9	low	low	moderate	moderate	moderate	low	low	moderate
Vogelberg (2007) (14)	3	2	2	7/9	low	low	moderate	low	low	moderate	low	low

421 **FIGURE LEGEND** Figure 1: Flow diagram of studies from search to inclusion in the systematic review

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