Association of physical activity and cardio-respiratory function or BMI and body composition in preterm born individuals: a systematic review

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Short title: Physical activity in preterm born individuals

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ABSTRACT

AIMS:

To evaluate the association of physical activity (PA) and forced expiratory volume in 1 second (FEV1), peak oxygen consumption (pVO2), body mass index (BMI) and body composition in preterm born individuals.

Methods:

Cochrane Library, EMBASE, MEDLINE, AMED, ERIC, Web of Science and PsycInfo were searched with no restriction on language and date of publication from inception to January 2018. Data were extracted comparing preterm born individuals with different frequencies of PA and the outcome of interest.

Results:

One randomized controlled, two longitudinal and thirteen cross sectional studies comprising 1922 preterm born individuals aged 5-25 were included. Assessment varied from a PA program to accelerometer data, interviews and self-report questionnaires. In preterm born children, more PA was associated with better cardio-respiratory function in those groups with impaired lung function or with lower BMI in those groups with increased risk factors, but no association was found in unimpaired children. In preterm born adults, more PA was associated with higher pVO2 and lower BMI.

Conclusion:

Only tentative conclusions can be drawn, especially regarding differences of the association of PA between preterm and term born populations. Further studies are needed to analyse the association of PA in preterm born individuals with reduced cardio-respiratory function.

Key words

Infant, premature; Physical activity; lung function; peak oxygen consumption; Body Composition

"Key Notes"

1. Lower forced expiratory volume (FEV1) is associated with less physical activity, but only in preterm born individuals with impaired lung function.
2. The association of physical activity and exercise capacity (pVO2) seems similar in preterm and term born individuals.
3. Vigorous PA is associated with lower body mass index (BMI) in term but not preterm born adolescents.

Preterm birth can be regarded as a chronic health condition that has the potential to lead to functional limitations(1) like intellectual disability, cerebral palsy, other motor problems(2) and psychiatric conditions(3). Additionally research has shown an increased risk of impaired lung function(4), reduced cardiorespiratory fitness(5) and more cardio-metabolic risk factors(6).

The World Health Organisation recommends physical activity (PA) to improve cardio-respiratory function and to lower the cardio-metabolic risk in children(7) and adults(8). The most frequently reported measure of lung function in relation to PA is the forced expiratory volume in 1 second (FEV1). Lower values are an indicator for impaired lung function with obstruction of the lower respiratory system. Higher FEV1 has been found in athletes(9), as well as in children(10) after a high intensity training. PA is recommended for patients with chronic obstructive pulmonary disease in line with standard healthy living advice(11) and higher levels of PA have been associated with a lower age-related decline in lung function(12). Peak oxygen consumption (pVO2) reflects the cardiorespiratory fitness of an individual and is widely used as an indicator for health. Cardio-respiratory fitness increases with PA in all age groups although at younger age pVO2 changes are lower than in adults (13).

Since preterm born individuals have been found to suffer from higher cardio-respiratory and cardio-metabolic risk they might especially profit from PA as a preventive intervention. However, the pathophysiologic basis for impaired cardio-respiratory function and increased cardio-metabolic risk differs in preterm born compared to other populations. For example, chronic obstructive pulmonary disease is the second most frequent(14) though heterogeneous pulmonary disease(15) in adults. Smoking related changes are the most common aetiology while preterm born individuals show a distinct phenotype with possibly an impaired function of the more proximal conducting airways(16, 17) and/or an alveolar hypoplasia and impaired vascular development(18) being discussed as aetiologies. Because of this different aetiology preterm born individuals might react differently to PA compared to pulmonary diseases of other aetiologies. Regarding cardio-metabolic risk factors preterm and term born adults have similar body mass index (BMI: weight in kg/height in m^2) with a large heterogeneity (19), however they seem to differ in their body composition with preterm born individuals having less lean body mass(6). These differences may influence the associations of PA and BMI or body composition.

Participation in PA is often recommended during follow-up-visits of preterm individuals. However, it is not clear whether any of the above mentioned health outcomes can be improved by PA in preterm born individuals. A US study described for example a positive association for PA and cardio-respiratory function (20) but none were found in a Norwegian study of preterm born children(21) at age 10. A reduced BMI but increased body fat percentage (fat mass in kg/weight in kg) has been described with more PA(22) in preterm born adults. Thus findings on the association of PA with health indicators in the preterm born population are controversial.

The aim of this systematic review was to assess the association of PA in preterm born individuals with cardio-respiratory function (pVO2, FEV1) and BMI and body composition.

METHODS

The systematic review was registered on Prospero (registration no CRD42018079736). Methods were developed according to the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(23).

Search strategy

A literature search was conducted in January 2018 and repeated in August 2018. The following electronic databases were searched: Cochrane Library, EMBASE, MEDLINE, AMED, ERIC, Web of Science and PsycInfo. No restrictions were used for language or publication date. The key words used were as follows: (leisure or recreation or physical activit* or fitness or sport or motor activit* or run* or swim* or walk* or exercise or game*) AND (low birth weight or prematur* or preterm*) AND (child* or adolescent* or adult*) AND either (lung or VO2 or respiratory or aerobic capacity) for cardio-respiratory outcome or (metabolic or body mass or lean body or fat free or fat mass or body fat) for cardio-metabolic outcome. Duplicates were removed using the EndNote® bibliographic software.

Study Selection

We included studies of children (age 2 to 17) or adults (age 18 and above) born at a gestational age of less than 37 weeks that analysed cardio-respiratory function (FEV1, pVO2) or BMI and body composition with regard to PA. We excluded studies that only reported low birth weight.

Abstracts, editorials, commentaries, letters, and study protocols were excluded but reviewed for possible references. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources were screened independently by two reviewers (JS and RE) to identify studies that potentially met the inclusion criteria outlined above. Any disagreement between reviewers over the eligibility of particular studies was resolved through joint discussion. Inter-rater agreement was high (cardio-respiratory title ƙ=0.95 and abstract ƙ=0.97; cardio-metabolic title ƙ=0.97 and abstract ƙ=0.91). The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by JS and RE. Citations were traced, and where multiple reports of the same cohort existed, the study reporting the largest sample number was used.

Data extraction and synthesis

Data on the study design, characteristics of the sample (sample size, gestational age, age at report), form of assessment of PA, and data of the analysed outcome parameter were extracted from the included studies and recorded in standard data extraction forms.

Quality assessment

JS and RE assessed independently the methodological quality of included studies according to the modified *Newcastle-Ottawa Scale* as used by Parkinson et al(19). The modified Newcastle-

Ottawa Scale assesses the quality of case-control or cohort studies in term of the selection, comparability and outcome assessment. The total rating score ranges from 0 to 7 “stars”, with 7 indicating the highest quality.

RESULTS

The PRISMA flow chart of search results is shown in figure 1. We identified 1979 (cardio-respiratory) and 1150 (BMI and body composition) publications with another four publications added after screening of reference lists. A total of 9 studies for cardio-respiratory function and 7 studies for BMI and body composition were included. Data extracted from the studies are shown in table 1 (cardio-respiratory function) and table 2 (BMI and body composition). A short summary of findings with regard to the association between PA and FEV1, pVO2, BMI or body composition is shown in table 3.

The mean score of quality assessment for all included publications was 5.6 (Supplement table S1).

Assessment of PA

In childhood, PA was measured using objective as well as subjective methods. One randomized controlled trial(24) examined the effect of a 4 week PA program. Accelerometer data were used in three studies analysing three different outcomes (25-27). The amount of vigorous PA was determined via interview analysing two different outcomes(20, 28). All other studies in childhood used different instruments giving times or duration per week with exercise, participation rates in club sport or activity ratings compared to peers.

In adults, PA was determined via questionnaires giving times or duration per week of PA(22, 29, 30) with only one study differentiating the intensity of PA(31).

Since PA was assessed in a heterogeneous manner across the different studies it was not possible to conduct quantitative analysis on data to perform a meta-analysis. Data are presented as a systematic review.

Cardio-respiratory function

Studies reporting on correlations between PA and pVO2 or FEV1 included preterm born individuals from 5 to 25 years (table 1). Detailed descriptions of each study and their results are shown in supplement table S2 and S3.

FEV1

No association of PA and FEV1 was found in studies of preterm born individuals with a FEV1 within the normal reference range. Barcelona(24) was the only study that randomized preterm born children (age 5) with Bronchopulmonary Dysplasia (BPD) to a group-PA program twice a week for four weeks. FEV1 improved in the intervention group, but pre- and post-intervention ΔFEV1 did not differ significantly between intervention and control group. ALSPAC(25) was the only longitudinal study included in this review and no significant correlations between PA at age 11 (accelerometer data) and FEV1 at 8 years(32) was found in any gestational age group analysed. The Norway 91(21) (age 10) and SIENA(33) (age 16) studies with children and the Norway 82(29) with adults (age 25) found no association between frequency of PA and FEV1.

The PILOT (age 8), DEX-Trial (age 9) and CARDIFF-Study (age 10) analysed preterm born children with a median FEV1<85%. The Dex-Trial and CARDIFF-Study showed a moderate correlation with a better FEV1 in children engaging in more PA(20, 34). The PILOT study(35) reported no correlation of PA and FEV1. However, the correlation analysis relied on 11 children while FEV1 was assessed for the whole group of 15 children and no missing-value analysis is shown. Therefore, it is unclear, whether the group analysed truly represented children with a median FEV1 below 85%.

Separate analysis of preterm and term born children for the association of PA and FEV1 was not shown in any study.

pVO2

In preterm born children, two studies analysed groups with normal pVO2. In neither study (PILOT Study(35) (age 8), NORWAY 91(21) (age 10)) was PA associated with pVO2.

In preterm born children, two studies analysed groups with reduced cardio-respiratory fitness. Barcelona(24) analysed the effect of a 4-week randomized controlled PA program using the incremental shuttle walk test(36) in preterm born children with BPD (age 5). The EPICURE cohort(26) analysed the correlation of accelerometer data with pVO2 (age 11). Both studies showed better cardio-respiratory fitness in children engaging in more PA.

In preterm born adults, the NORWAY 91(30) and NORWAY 82(29) study reported a positive association of PA and pVO2 in very preterm and term born controls at age 18 and 25 but did not state the effect size.

Separate analysis of preterm and term born individuals for the association of PA and pVO2 was shown in two childhood(21, 26) and two adult studies(29, 30) with similar effects in preterm and term born groups.

BMI and body composition

Studies reporting on associations between PA and BMI or body composition in preterm born individuals included participants aged 11 to 23 years (table 2). Detailed descriptions of each study and their results are shown in supplement table S4 and S5.

BMI

In preterm born adolescents with normally distributed BMI neither the GROWMORE-Study(27) (age 16) nor the Forsyth Study(28) (age 15) found an association of PA and BMI. The GROWMORE-Study showed results for moderate but not for vigorous PA. In preterm adults with normally distributed BMI the HeSVA(22) study found that higher frequency of PA showed an association with a lower BMI.

In preterm born cohorts with increased rates of obesity, two studies analysed the association of PA and BMI. The MLS (37) analysed longitudinal data for PA between age 8 and 11 in preterm born children and controlled the outcome (obesity/overweight) for birth weight. The Wave VIII (31) analysed preterm born adults. Both studies reported association of less PA with higher BMI. In the child cohort the obesity risk was doubled in physically in-active children, the adult study reported a small effect size of more PA on BMI.

Separate analysis of preterm and term born individuals for the association of PA and BMI was only shown in the Forsyth Study(28). While in preterm born adolescents no association of PA and BMI was noted, term born adolescents showed a moderate association of more vigorous PA and lower BMI.

Fat mass

The Oklahoma study(38) found a higher fat mass but also higher lean body mass in all physically active preterm born children. However, this was confounded by age and the association disappeared after adjusting for age.

Body fat percentage

In preterm adolescents, the Forsyth study(28) reported a moderate association of more vigorous PA and lower body fat percentage. In preterm born adults, the HeSVA study (22) found the opposite: a lower frequency of physical activity was associated with a lower body fat percentage.

Fat mass index

The Forsyth(28) (age 15) and CIKL study(39) (age 11) reported a small to moderate association of higher physical activity level with lower fat mass index (FMI: fat mass in kg/height in m^2) in preterm and term born adolescents while the GROWMORE study(27) (age 16) reported no association of accelerometer data and FMI with a cut off at moderate activity levels (>2294 counts/ minute).

Separate analysis of preterm and term born individuals for the association of PA and body-composition was only shown in the Forsyth Study(28) and similar in preterm and term born groups for body fat percentage and FMI.

DISCUSSION

Preterm born individuals make up 10.6% of birth world-wide(40) and they are prone to adverse cardio-respiratory outcomes (4, 5) and increased cardio-metabolic risk factors(6). Even though the benefits of physical activity are propagated in health policies(7, 8), this systematic review reveals a paucity of studies with preterm populations. Furthermore, large variations by age, not comparable measurements of PA, missing data of not significant correlations and missing effect sizes precluded quantitative meta-analysis. Since most studies used a cross sectional study design, it was also not possible to determine the direction of the association between PA and the health variables. The included studies reported mainly on very preterm born individuals and comparison across the different gestational age groups was not possible. The only comorbidity frequently controlled for was BPD. However, coordination disorder(2) occurs at an increased rate in the preterm population and thus might also influence participation in PA(41) and the association of PA with health outcomes. Overall, there was weak evidence that PA improves cardio-respiratory function or BMI or body composition in the preterm population. Due to the methodological limitations, results need to be interpreted cautiously.

This systematic review showed that observed differences depended on the age group analysed for the association of PA with BMI and body composition. While there was no association between PA and BMI (27, 28) for preterm born children or adolescents, more PA was associated with lower BMI(22, 31) in preterm born adults, with a similar effect size as described in the general adult populations(42). Pooled twin studies have shown that the heritability of BMI decreases with age, while the influence of environmental factors increases with age(43), which might explain these age related results. This is supported by conflicting evidence about the association of PA and BMI in childhood in general (44-46), while data in adults show an association of lower BMI with more PA (47). In longitudinal adult studies PA has been shown to decrease BMI(48), while longitudinal childhood studies showed reverse causality with obesity leading to inactivity (49). Therefore, data reported in preterm studies included in this review are consistent with the existing literature in the overall population.

Observed differences of the association of PA in childhood with FEV1, pVO2 and BMI were sample dependent. All studies in preterm born children with an abnormal distribution of the outcome parameter showed a correlation of PA with FEV1(20, 34) or cardio-respiratory fitness(24, 26) or BMI(37). Preterm born children with FEV1 below the reference range have an impaired lung function most likely due to either alveolar hypoplasia and impaired vascular development or an impaired function of the more proximal conducting airways(17). The direction of the association is unclear and longitudinal studies are warranted. The association might be bidirectional as has been described in cystic fibrosis where the degree of pulmonary impairment influences participation in PA(50) but at the same time those with more participation in PA show a slower decline of lung function (51). Only one study(35) reported a mean FEV1<85% and did not find an association between PA and FEV1. However, due to high rates of missing values and no missing value analysis, study findings are uncertain.

Most preterm studies showed a reduced FEV1 compared to reference values or the term control group as is consistent with the literature(4). However, a reduced FEV1 within the normal reference values did neither seem to limit PA(25) nor did it seem to be improved by PA as analysed in cross sectional studies. Similarly in adolescents with healthy lung function(52) no association of PA with FEV1 was seen and children with asthma did not differ from non-asthmatic in PA(53). However, an already marginally reduced FEV1 in childhood in the preterm born population increases the risk for early pulmonary decline. Therefore, it would be important to investigate whether the decline due to aging can be influenced by PA in preterm born individuals with marginally reduced FEV1 similar to the effect seen in cohort studies(12). These studies need to be designed to cover decades instead of years.

The association between PA and outcomes was rarely analysed separately for preterm and term born groups. It might suggest that findings for those born preterm and full term of the associations of PA with pVO2(26, 29, 30) do not differ. Just one study(28) analysed the association of PA with BMI/body composition. Here a difference was noted regarding BMI but not body fat percentage or FMI. These observed differences in BMI require replication. Until more data are available the association of PA with BMI or body composition should be analysed stratified by gestational age groups.

This review was limited by the variety of PA assessments. Future studies should assess frequency and intensity(54) for all outcomes as well as type of PA (endurance versus power or skill sport (9, 11)) for FEV1. Children unlike adults have more difficulty with recall ability for self-reported PA questionnaires(55). Therefore, vigorous PA might be better quantified during childhood by accelerometer(56) than by a questionnaire.

CONCLUSION

There is a surprising paucity of studies of the association of PA and cardio-respiratory function or BMI and body composition in preterm children. Only tentative conclusions are possible and more studies are needed that measure PA in a standard and comparable format. Preliminary results indicate that more PA is associated with less obesity/overweight or lower FMI in preterm born children and higher pVO2 or lower BMI in preterm born adults. Preterm born individuals with reduced FEV1 engage in less PA than full term born and longitudinal studies or RCTs are needed to determine the direction of this association. Association of PA and body composition are dependent on age of measurement as well as preterm birth and stratified analysis is recommended. On current evidence paediatricians should follow the WHO recommendations of 60 minutes moderate to vigorous PA per day(7) also for preterm children with impaired lung function.

Abbreviations

BMI	body mass index
BPD	bronchopulmonary dysplasia
FEV1	forced expiratory volume in first second
FMI	fat mass index
PA	physical activity
PT	preterm
pVO2	peak oxygen consumption

CONFLICT OF INTEREST/FUNDING

The authors have no conflict of interest to declare. JS was financed by a research fellowship from the DFG (Deutsche Forschungsgemeinschaft) grant no: SP 1731/1-1 and RE, MM and DW supported by the European Union's Horizon 2020 research and innovation program under grant agreement No: 733280

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Figure 1: PRISMA 2009 flow diagram of literature search. (A) cardio-respiratory outcome, (B) BMI or body composition outcome

Table 1: Summary of studies included in systematic review on the association between physical activity and cardio-respiratory function

PT: preterm; FT: full term; EP: extremely preterm; VP: very preterm; MP: moderately preterm; LP: late preterm; VLBW: very low birth weight (<1500g); pVO2: peak oxygen consumption; FEV1: Forced expiratory volume in 1 second; GA: gestational age given as mean (±SD) or median (25th-75th centile). ISWT: incremental shuttle walk test, IG:intervention group with PA program, CG: control group. Nixon giving GA and age as median (5th-95th centile). PA: physical activity, MVPA: accelerometer data moderate to vigorous activity; EEE: estimated energy expenditure; DEX: treatment group receiving dexamethason postnataly

Table 2: Summary of studies included in systematic review on the association between physical activity and BMI or body composition

BPD: bronchopulmonary dysplasia; PT: preterm; FT: full term; VLBW: very low birth weight (<1500g); VP: very preterm; LMP: late or moderate preterm; BMI: Body mass index; FMI: fat mass index; BF%: body fat percentage; LBM: lean body mass, FM: fat mass; GA: gestational age given as mean (±SD) or median (25^{th}-75^{th} centile) for the preterm born group. Redman giving GA and age as median (5th-95th centile); PA: physical activity, inadequate PA (<5x30min. per week at >2 visits age 8,9,10 or 11); PA level CIKL: compared to peers (less, same, more, much more), Oklahoma: sedentary (sed.), moderately active (mod.), active.

Table 3: Summary of associations of physical activity in preterm born children and adults for FEV1, pVO2, BMI and body composition

PA: physical activity. FMI: Fat mass index
[1]abnormal FEV1: median/mean of the analysed group below 85% predicted.
[2]abnormal pVO2: mean/median <39ml/kg/min (or for boys 42ml/kg/min, for girls 35 ml/kg/min)(57), ISWT mean<75% predicted.
[3]abnormal BMI: median/mean >25kg/m^2 in adults, or >⅓ overweight or obese children.
[4]the reported mean FMI or body fat percentage of the study group was never above the 85th centile for the respective age group; therefore, none of the studies were classified as “abnormal” distribution of body composition.
Effect sizes are given if they could be classified with the available data.

Table S1: Modified Newcastle-Ottawa scale for study assessment of methodological quality

Stars were awarded if the study met the specified criteria (highlighted in light gray). The total rating score ranges from 0 to 7 “stars”, with 7 indicating the highest quality.

Table S2: Physical activity and FEV1: description of included studies and their results

Table S3: Physical activity and pVO2: description of included studies and their results

Table S4: Physical activity and body mass index: description of included studies and their results

Table S5: Physical activity and body composition: description of included studies and their results