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Long-term expiratory airflow of infants born moderate-late preterm: A systematic review and meta-analysis

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Summary

Background Moderate-late preterm (MLP; 32 to <37 weeks' gestation) birth is associated with reduced expiratory airflow during child, adolescent and adult years. However, some studies have reported only minimal airflow limitation and hence it is unclear if clinical assessment in later life is warranted. Our aim was to compare maximal expiratory airflow in children and adults born MLP with term-born controls, and with expected norms.

Methods We systematically reviewed studies reporting z-scores for spirometric indices (forced expired volume in 1 second [FEV_1], forced vital capacity [FVC], FEV_1/FVC ratio and forced expiratory flow at 25-75% of FVC [$FEF_{25-75\%}$]) from participants born MLP aged five years or older, with or without a term-born control group from 4 databases (MEDLINE, CINAHL, Embase, Emcare). Publications were searched for between the 22nd of September 2021 to the 29th of September 2021. A meta-analysis of eligible studies was conducted using a random effects model. The study protocol was published in PROSPERO (CRD #42021281518).

Findings We screened 4970 articles and identified 18 relevant studies, 15 of which were eligible for meta-analysis (8 with term-born controls and 7 without). Compared with controls, MLP participants had lower z-scores (mean difference [95% confidence interval] I^2) for FEV_1: -0.22 [-0.35, -0.09] 49.3%, FVC: -0.23 [-0.4, -0.06] 71.8%, FEV_1/FVC: -0.11 [-0.20 to -0.03] 9.3% and $FEF_{25-75\%}$: -0.27 [-0.41 to -0.12] 21.9%. Participants born MLP also had lower z-scores, on average, when compared with a z-score of 0 (mean [95% CI] I^2) for FEV_1: -0.26 [-0.40 to -0.11] 85.2%, FVC: -0.18 [-0.34 to -0.02] 88.3%, FEV_1/FVC: -0.24 [-0.43 to -0.05] 90.5% and $FEF_{25-75\%}$: -0.33 [-0.54 to -0.20] 94.7%.

Interpretation Those born MLP had worse expiratory airflows than those born at term, and compared with norms, although reductions were modest. Clinicians should be aware that children and adults born MLP may be at higher risk of obstructive lung disease compared with term-born peers.

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Keywords: Preterm; Moderate-late preterm; Pulmonary function; Spirometry; Expiratory airflow

Research in context

Evidence before this study

It is now well recognised that those born extremely preterm (<28 weeks' gestational age) and very preterm (28 to <32 weeks' gestational age) have lower expiratory airflows later in life compared with their term-born peers. However, it is less clear if infants born moderate-late preterm (32 to <37 weeks' gestational age) also experience similar reductions in expiratory airflows during school-age or adult years.

Added value of this study

This meta-analysis of aggregate-level data provides compelling evidence that those born moderate-late preterm have poorer expiratory airflow compared with term-born controls and population norms (i.e. z-score of 0). However, reductions were modest for children and adults.

Implications of all the available evidence

While moderate-late preterm infants attain more favourable expiratory flows than those born extremely preterm or very preterm, they may still be at higher risk of developing chronic obstructive pulmonary disease later in life compared with term-born individuals.

Introduction

Preterm birth is associated with increased respiratory morbidity during infancy, and impaired expiratory airflow later in life.[1–3] The incidence of moderate late-preterm (MLP) birth, defined as birth between a gestation of 32 to < 37 weeks, has steadily increased over the previous decade. For example, the Australian MLP preterm birth rate has increased by a relative 6.2% between 2009 to 2019, accounting for 6.9% of all live births in 2019.[4,5] A similar pattern has been observed in the United States (US), where the MLP preterm birth rate has risen by 3.7% over the same period.[6] The increase in the MLP birth rate has been simultaneous with advancing maternal ages and better obstetric surveillance.[4–6] As infants born MLP vastly outnumber very preterm (VP; 28 to <32 weeks' gestation) and extremely preterm (EP; <28 weeks' gestation) survivors, morbidity in those born MLP may result in substantial economic and healthcare burden.[7]

Compared with infants born at term, infants born MLP are at an increased risk of developing adverse respiratory sequelae, such as asthma and recurrent wheeze.[1,8] It is becoming increasingly evident that birth during the 32 to <37 week gestational window interrupts a time critical period of rapid *in utero* respiratory growth. During the saccular and alveolar phase of gestation, acinar structures undergo a period of maturation which is characterised by peripheral airway enlargement, decreasing air-space wall thickness, and increasing alveolar surface area.[9,10] Deviation from this finely programmed series of normal lung development may cause alterations in pulmonary mechanics during infancy, resulting in an overly compliant chest wall, reduced expiratory airflow and increased airway resistance at birth.[11–13]

Structurally immature bronchial and parenchymal networks, in addition to incurred respiratory morbidity during infancy, may have adverse effects on pulmonary function later in life.[3] Recent data from prospective birth cohort studies have reported an association between MLP birth and reduced expiratory airflow during school age and adolescent years, which persists into early adulthood.[14–16] However, studies have reported varying degrees of airflow limitation and therefore the trajectory of expiratory airflow for infants born MLP remains unclear. Our study aims to compare maximal expiratory airflows in children and adults born MLP with term-born controls, and with expected norms.

Methods

Protocol and registration

Our study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[17] and the study protocol is published in PROSPERO International Prospective Register of Systematic Review (CRD #420212815 18).

Study selection

Published studies met inclusion criteria if they reported z-scores for the spirometric indices of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC or forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$) from participants aged 5 years or older who were born MLP. If studies included data obtained from age-matched term-born controls, comparison was made between MLP and term-born participants. A language

restriction was not placed on the literature search, although to sufficiently assess the quality of each study we required the full text to be available in English. Studies published between January 1984 and September 2021 were eligible for inclusion in the review. Studies that reported outcomes in absolute units or percent predicted, or reported pulmonary function measurements other than spirometry were ineligible for meta-analysis but were eligible for review. Studies were excluded if data obtained from MLP participants could not be differentiated from EP or VP participants.

Data sources and searches

Relevant studies were identified by searching 4 electronic databases (MEDLINE, CINAHL, Embase and Emcare) between the 7th of September 2021 to the 21st of September 2021. A repeat search was conducted on 28 January 2022. We conducted 3 discrete searches for each database using terms specific to preterm birth and pulmonary function testing. The complete search strategy is available in e-Appendix #1 of the online supplementary material. Using the inclusion criteria, two independent authors (C.D.B and C.N) removed duplicates, screened the titles and abstracts of retrieved articles and obtained full-text articles. A third author (L.W) resolved any dispute. When studies reported outcomes from the same cohort in two separate articles, data from the first time point were used. Explanations for study exclusion at full-text screening are available in e-Appendix #2.

Data synthesis and analysis

Z-scores of spirometric indices from eligible studies were extracted for meta-analysis by two authors (C.D.B and C.N). A third author (L.W) verified the data extracted. Authors were contacted for aggregate-level data if a study did not report indices of spirometry as z-scores derived from the Global Lung Initiative (GLI) reference equations.[18] Authors were also contacted if a study reported indices of spirometry obtained from a combination of both VP and MLP born participants. In such instances, only aggregate-level data from MLP born participants were requested. Additionally, authors were contacted when a spirometric index of interest was recorded but not reported. Responses from contacted authors were considered until January 11, 2022. For longitudinal studies that presented cohort data at multiple time points, data from the first time point were used.

STATA version 17.0 (StataCorp, 2021) was used to analyse data. Meta-analysis was conducted using the *metan* statistical analysis package.[19] Birth and perinatal characteristics of participants, sample size, pulmonary function tests performed and spirometry reference values were summarised for each study (Table 1). For each study, the mean z-score and standard deviation for FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$ in addition to number of participants were extracted for MLP and term-control groups.[20] In cases where the mean and standard deviation were not reported, the median and interquartile range (IQR) were used instead if sample sizes were larger than 25 participants in each group.[21] If z-scores were presented for separate gestational age (GA) groups within the 32 to <37 week gestational period, means and standard deviations for each group were combined in accordance with the Cochrane handbook for systematic reviews.[22]

Separate meta-analyses were performed for studies that included term-born controls only and for all studies. For studies with term-born controls, mean differences in z-score of FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$ between MLP participants and term-born controls were estimated. For all studies, mean z-scores from all MLP participants were estimated and compared with the population mean (i.e., a z-score of 0). An assumption was made that the population mean used for each study reflected the most up to date reference equations available at the time of publication. Overall estimates were obtained using a random effects model, with between-study variability estimated using the Empirical Bayes method. Results from the meta-analysis are presented with study weight (%), 95% confidence interval (CI), Z values, P values and heterogeneity statistics (I^2). A funnel plot and Egger's test were used to assess the risk of publication bias when there were at least 10 or more studies included in the meta-analysis.[23,24] If outcomes could not be obtained as GLI z-score, studies were still eligible for inclusion in the meta-analysis but were subject to a sensitivity analysis.

Quality assessment

Studies of cohort or case control design were assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies or the NOS for case control studies.[25] For cohort studies, we considered that participants lost to follow-up were unlikely to introduce bias if follow-up rates were ≥80%, or between 70% and 80% with an accompanying statement describing those lost to follow up. Cross sectional studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for analytical cross sectional studies,[26] while version 2 of the Cochrane risk-of-bias tool was utilised to evaluate studies of randomised controlled trial (RCT) design.[27]

Role of funding sources

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

Study	Region	MLP Birth Characteristics					Sex (% Male)		Assessment						
		Gestational Age (wk)			Birthweight (g)		MLP	Term	MLP Age (years)			No. of Participants		Pulmonary Function Tests Conducted	Spirometry Reference Values
		Mean	SD	Range	Mean	SD			Mean	SD	Range	MLP	Term		
Aoyama et al, 2021[31] [a]	USA	33.9	1.3		2189	592	72	NA	7.3	1.8		7	NA	Spirometry	GLI 2012
Arroyas et al, 2020[36]	Spain	34.2	1.2		2014	526	51.4	NA	14.1			74	NA	Spirometry FeNo	GLI 2012
Carbonell-Estrany et al, 2015[32] [a]	Spain	33.6 [b]	0.8 [b]		2022 [b]	362 [b]	56.5 [b]	NA			6-7	236	NA	Spirometry Post BD Spirometry	GLI 2012
Dantas et al, 2021[28]	Brazil	34	1.7		NR	NR	23.1	40.8	7.9	1.4		52	71	IOS	NA
Gonçalves et al, 2016[33] [a]	Brazil	34	1.4		1635	248	41	NA	10.1	2.1		46	NA	Spirometry	GLI 2012
Kaczmarczyk et al, 2017[37]	Poland	34.5	1.9		NR	NR	0	0	28.1	2.4		12	27	Spirometry	GLI 2012
Kotecha et al, 2012[14]	UK	35.2	1		2588	427	55	49	8.7	0.3		317	6144	Spirometry Reversibility	Chinn et al, 1992
Landry et al, 2016[38] [a]	Canada			32-36	NR	NR	42	25	21.4	1.8		12	8	Spirometry Post BD Spirometry DLCO Plethysmography Methacholine	GLI 2012
Morta-Alba et al, 2019[29]	Spain			32-35	1942	384	NR	NA			6-8	116	116	Spirometry FeNO	Not specified
Narayan et al, 2013[39] [a]	UK	35.2	1.2		NR	NR	NR	NR	12	1.1		21	61	Spirometry Plethysmography	GLI 2012
Näsänen- Gilmore et al, 2018[16] [b]	Finland	35.1	1.4		2494	497	49	48.1	23.2	1.2		321	341	Spirometry Post BD Spirometry	GLI 2012
Pérez-Tarazona et al, 2021[34]	Spain	34	1.1		1983	526	55	NA	14.5	0.7		102	NA	Spirometry Post BD Spirometry DLCO Plethsmography	GLI 2012
Scheltema et al, 2018[35] [a]	NLD			32-35	2292 [b]	NR	54	NA	5.9	0.4		335	NA	Spirometry Post BD Spirometry	GLI 2012
Thunqvist et al, 2016[15] [a]	Sweden	35		32-36	2603	495	44	51	16.4	0.4		99	1564	Spirometry IOS	GLI 2012
Todisco et al, 1993[30]	Italy	34.9	1.1		1980	450	62	55	11.6	2.5		34	34	Spirometry Plethysmography Methacholine Nitrogen SBW	NA

Table 1 *(Continued)*

Study	Region	MLP Birth Characteristics					Sex (% Male)		Assessment					
		Gestational Age (wk)			Birthweight (g)		MLP	Term	MLP Age (years)			No. of Participants		Pulmonary Function Tests Conducted	Spirometry Reference Values
		Mean	SD	Range	Mean	SD			Mean	SD	Range	MLP	Term		
Vrijlandt et al, 2018[40 a]	NLD	34	1		2442	539	57	53	13.6	0.6		37	34	Spirometry MBW CPET	GLI 2012
Yaacoby-Bianu et al, 2019[41]	Israel	35	0.9		2336	400	59	50	8.2	1.7		29	30	Spirometry MBW	GLI 2012
Yammine et al, 2016[42 a]	CHE	33.4	0.78		1969	579	58	47	9.3	1.3		12	46	Spirometry MBW	GLI 2012

Table 1: **Characteristics of included studies, listed alphabetically by first author.** [14–16,28–42]

Abbreviations: BD, Bronchodilator; CHE, Switzerland; CPET, cardiopulmonary exercise test; DLCO, diffusing capacity in 1 second for carbon monoxide; FeNO, fraction of exhaled nitric oxide; GLI, global lung initiative; IOS, impulse oscillometry; MBW, multiple breath washout; MLP, moderate-late preterm; NA, not applicable; NLD, The Netherlands; NR, not reported; PFT, pulmonary function test; SBW, single breath washout; SD, standard deviation; USA, United States of America; UK, United Kingdom.

[a] Data obtained from authors.

[b] Characteristics of cohort at birth (prior to participant loss to follow up assessment).

Results

Identified studies and study characteristics

The PRISMA 2020 flow diagram[17] for searched, identified, screened, and included records is presented in Figure 1. 4970 articles were identified from selected electronic databases after duplicates were removed. After screening the title and abstract of each article, 56 full-text articles were screened for eligibility. Once the responses from contacted study authors were collated, 18 articles satisfied the inclusion criteria.[14–16,28–42] 15 studies reported expiratory airflow data from MLP participants,[14–16,31–42] eight of which compared MLP participants with term-born controls.[14–16,37–42] Three studies were not eligible for meta-analysis, with two unable to provide z-score data,[29,30] and one with indices of impulse oscillometry only.[28] Of the 15 studies eligible for meta-analysis, 15 reported a z-score for FEV_1, FVC, and FEV_1/FVC with 13 reporting $FEF_{25-75\%}$. Though spirometry indices were not published as GLI z-score in five of the included studies,[14,33,35,38,39] these data were subsequently provided by four of the respective study authors.[33,35,38,39] We obtained aggregate-level MLP data from four studies that reported a combination of MLP and VP expiratory airflow data.[31,33,38,42] One study presented data as median and IQR.[41] A repeat literature search on 28 January 2022 did not reveal any additional studies eligible for inclusion in the review. Across the eight studies which reported spirometric indices from MLP and term-born participants that were eligible for meta-analysis, there were a total of 847 MLP participants and 8,209 controls.[14–16,37–41] An additional 819 MLP born participants were included in the seven studies without term-born participants,[31–36,42] resulting in 1,666 MLP born participants in total.

Birth and perinatal characteristics of participants, sample size, pulmonary function tests performed and spirometry reference values used are presented in Table 1. Included studies were published between 1993 and 2021 and varied in study design; observational cohort (n = 8),[14–16,29,37,38,40,42] cross-sectional (n = 8),[28,30,31,33,34,36,39,41] case control (n = 1)[32] and RCT (n = 1).[35] Three studies reported longitudinal spirometry measurements.[14,15,37] The age of participants born MLP ranged from 5 to 25 years; 15 studies reported pulmonary function outcomes obtained from school-aged children and adolescents,[14,15,28-34,36,39-42] while three reported outcomes obtained from adults.[16,37,38] Most studies included participants that were born between 32 to <37 weeks gestation (n = 14, 78%).[14–16,28,30,31,33,34,36–40,42] Three studies reported outcomes from those born 32 to <36 weeks[29,32,35] and another between weeks 35 to <37.[41] Studies were conducted mostly in high income countries (n = 16, 89%), and across a range of geographical locations; Europe (n = 13),[14,15,29,30,32,34–37,39,40,42] North America (n = 2),[31,38] South America (n = 2)[28,33] and the Middle East (n = 1).[41]

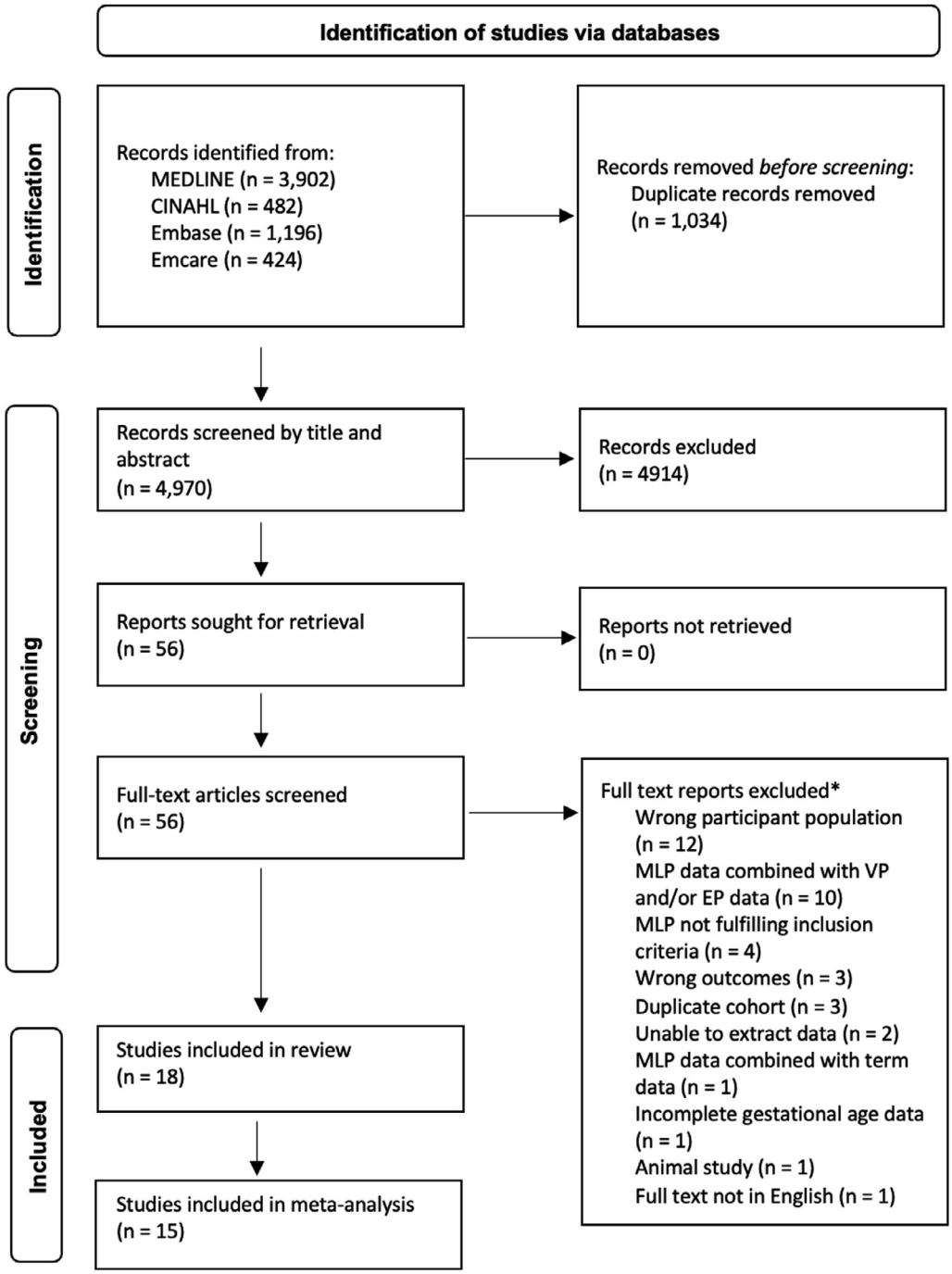


Figure 1. PRISMA 2020 flow chart of the searched, identified and included studies. Abbreviations: MLP = moderate-late preterm; VP = very preterm; EP = extremely preterm;
*Some studies satisfied more than 1 exclusion criterion.

Quality assessment

The highest attained rating using the NOS for cohort studies was 8/9 stars, achieved by one study.[14] The median score was seven stars, with a range of 5 to 7. Most participants from included cohort studies were representative of children and adults born MLP in the community (n = 6, 75%),[14–16,29,38,40] while matched controls were all chosen from the same community as participants born MLP. GA was ascertained from medical records in seven cohort studies,[14–16,37,38,40,42] while

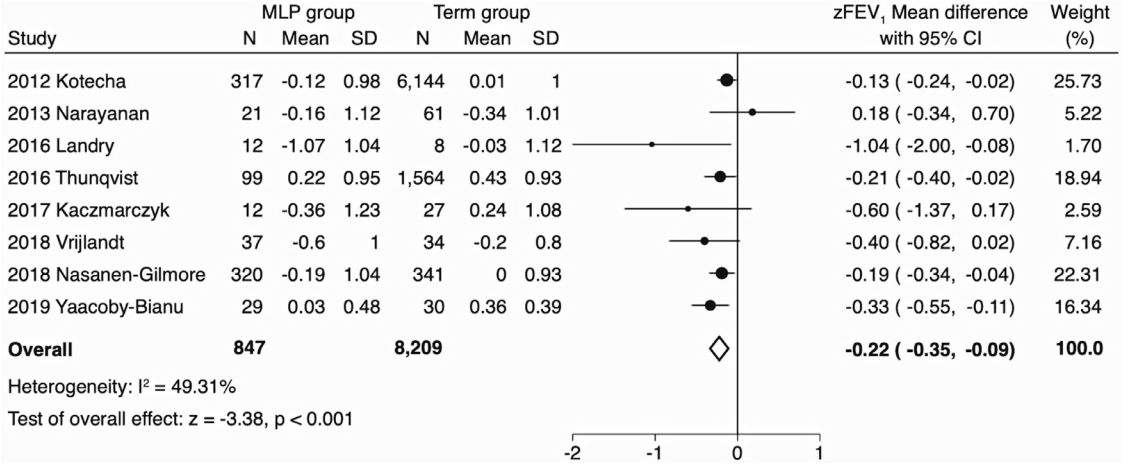


Figure 2. Forced expiratory volume in 1 second z-score ($zFEV_1$) of the moderate-late preterm (MLP) group compared with the term group. A mean $zFEV_1$ less than 0 indicates individuals born MLP are performing worse than the population of term-born controls, on average.

one study did not provide information on how preterm birth status was determined.[29] For all cohort studies, the pulmonary function of participants was not known upon study commencement.[14–16,29,37,38,40,42] Respective cohorts were age-matched in all studies. Most cohort studies (n = 5, 63%) controlled for an additional factor associated with pulmonary function in either study design or analysis.[14–16,38,42] Outcome assessment was poor; one study reported blinding of assessor to the gestational age of participants,[14] while another reported data collection by an independent assessor.[40] A follow-up duration of five years or more was reported in all cohort studies. Only one study reported a follow-up rate of ≥70% of the eligible cohort.[29] The case-control study achieved nine stars on the NOS for case control studies.[32]

Quality assessment of eight cross-sectional studies using the JBI appraisal checklist ranged from five to seven, with a median score of six. For all cross-sectional studies, the inclusion criteria, participants and setting were clearly described.[28,30,31,33,34,36,39,41] Most cross-sectional studies (n = 7, 88%) ascertained preterm birth status by medical chart review.[28,30,31,33,34,39,41] However, for all cross-sectional studies it was unclear if GA was measured using standard criteria, for example by ultrasound or parental reporting. Confounding factors associated with pulmonary function were identified for all cross-sectional studies, although only three studies implemented strategies to minimise the effect of these factors.[31,34,36] All cross-sectional studies measured pulmonary function in a valid and reliable way and used appropriate statistical analysis. The RCT was appraised

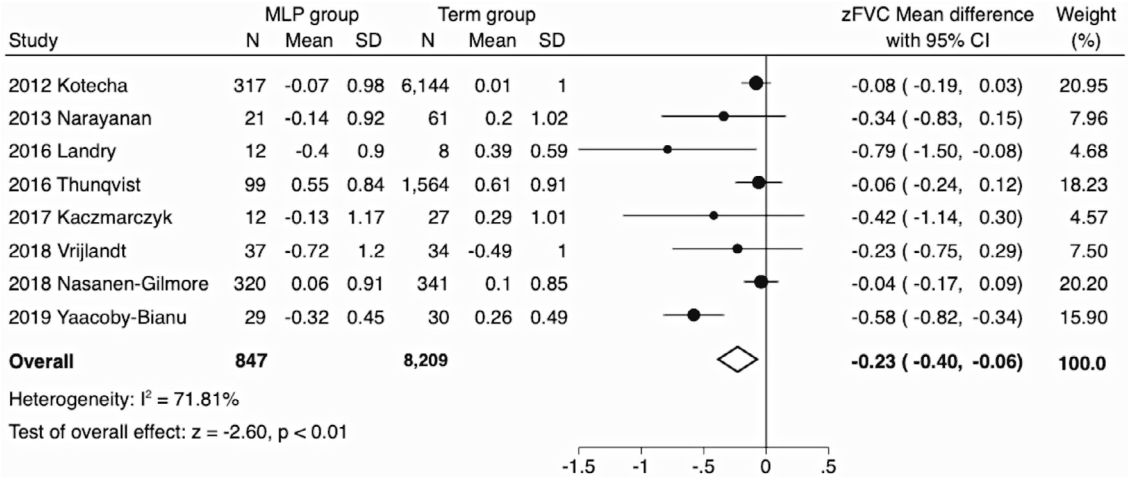


Figure 3. Forced vital capacity z-score (zFVC) of the moderate-late preterm (MLP) group compared with the term group. A mean zFVC less than 0 indicates individuals born MLP are performing worse than the population of term-born controls, on average.

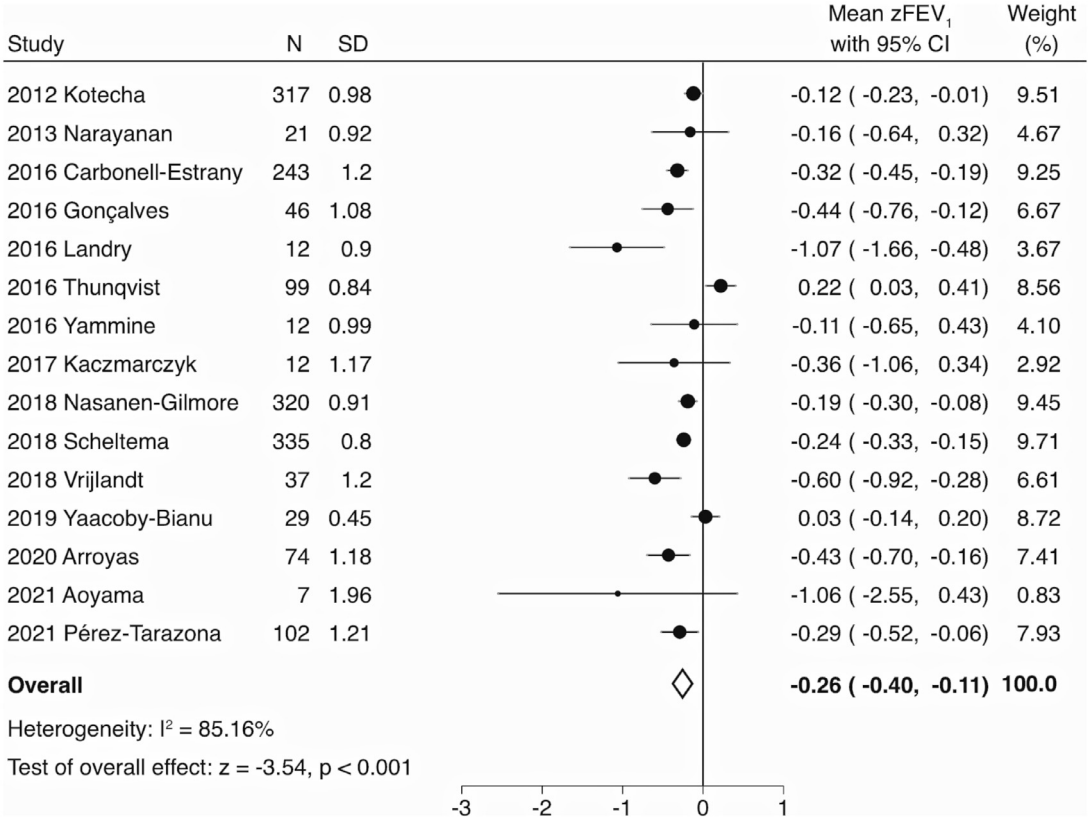


Figure 4. Forced expiratory volume in 1 second z-score (zFEV1) of the moderate-late preterm group compared with a z-score of 0. A mean $zFEV_1$ less than 0 indicates individuals born MLP are performing worse than population norms, as derived from relevant reference equations, on average.

as 'low risk' using the Cochrane risk-of-bias tool for randomised trials.[35] Quality assessment results for studies can be found in e-Appendix #3.

Synthesis of spirometry results

Compared with controls, participants born MLP had lower z-scores (mean difference [95% CI] I^2) for FEV_1: -0.22 [-0.35, -0.09] 49.3% (Figure 2), FVC: -0.23 [-0.40, -0.06] 71.8% (Figure 3), FEV_1/FVC: -0.11 [-0.20 to -0.03] 9.3% and $FEF_{25-75\%}$: -0.27 [-0.41 to -0.12] 21.9%. Participants born MLP also had lower z-scores, on average, when compared with population norms (mean [95% CI] I^2) for FEV_1: -0.26 [-0.40 to -0.11] 85.2% (Figure 4), FVC: -0.18 [-0.34 to -0.02] 88.29%, FEV_1/FVC: -0.24 [-0.43 to -0.05] 90.5% and $FEF_{25-75\%}$: -0.33 [-0.54 to -0.20] 94.8%. Supplementary forest plots are presented in e-Appendix #4. Similar results were also found when sensitivity analysis was conducted, excluding one study that did not present z-scores in GLI (e-Appendix #5). A sub-group analysis of those ≤ 18 years of age and studies of high quality only rendered similar overall estimates for all indices, except FEV_1/FVC (e-Appendix #6). Egger's test for a regression intercept produced a p-value 0.043, indicating potential publication bias (e-Appendix #7).

Discussion

This study provides compelling evidence that children and adults born MLP have worse expiratory flows than individuals born at term. A reduction across all spirometric indices was observed, indicating an impairment in pulmonary function. However, the degree of airflow obstruction was modest, evident by mean differences in z-scores of -0.22, -0.11 and -0.27 for FEV_1, FEV_1/FVC and $FEF_{25-75\%}$, respectively, when compared with term-born controls. Similar results were found when comparing spirometric indices with expected population mean z-scores of 0. Reductions in z-scores of these indices suggest that those born MLP are failing to catch up to normal physiological levels and therefore peak function.

Todisco et al published a study investigating pulmonary function in children born MLP in 1993.[30] The group performed spirometry and body plethysmography on 34 children born MLP, comparing them to matched term-born siblings. Despite similar expiratory

airflows between the two groups, MLP children were found to have elevated residual volumes and residual volume to total lung capacity ratios. In 2012 and 2016, longitudinal findings from respective Welsh and Swedish birth cohorts were published. A modest reduction of expiratory airflows in 8-9-year-old children born MLP was observed in both cohorts, however there are mixed results on whether this trend persisted to the ages of 16-17 years, with the Welsh cohort demonstrating an almost complete catch up to term-born controls,[14] while the Swedish cohort did not.[15] Despite recent interest in the long term pulmonary function of MLP infants, a very limited number of studies to date have investigated measurements of pulmonary function other than expiratory airflows. Two studies have conducted multiple breath washout in conjunction with spirometry in school-aged children and adolescent groups, respectively. Lung clearance index estimates were similar between participants born MLP and term-born controls.[40,41] Further to these findings, one of these studies also documented similar levels of exercise capacity between the two groups.[40]

Deficits in pulmonary function are more severe in children and adults born EP and VP than those born MLP. As such, the associations between gestational ages less than 32 weeks and reduced pulmonary function later in life are now well recognised. In 2012, findings from a meta-analysis provided evidence of an association between preterm birth and a reduced FEV_1 later in life. The meta-analysis included summary data from 22 studies, encompassing a total of 2085 and 3820 preterm and term-born controls, respectively.[2] In addition to the marked reduction in FEV_1, those born preterm who did not develop bronchopulmonary dysplasia (BPD) had more favourable FEV_1 outcomes later in life compared with those who did; an important observation given that BPD is uncommon among MLP newborns.[43] Importantly, these 22 studies collated data from a wide range of gestational ages (23 - 36 weeks). Consequently, it is difficult to determine the contribution of the MLP group to the overall findings of that study.

Preterm birth may increase the risk of developing chronic obstructive pulmonary disease (COPD) later in life, with EP and VP birth status now considered a potential risk factor.[44,45] A IPD meta-analysis published in 2019 demonstrated that VP survivors in early adulthood experience a mean reduction of -0.78 (95% CI -0.96, -0.61) in the z-score of FEV_1 compared with term-born controls.[44] Moreover, recent evidence indicates that middle-aged adults born moderate preterm during the pre-surfactant era experience impaired pulmonary function and therefore are at an increased risk of developing COPD compared with age-matched adults born late preterm and term.[45] While the risk of later life COPD is substantially lower compared with VP survivors, those born MLP should be made aware of the potential consequences preterm birth may pose to long-term respiratory health. Personal smoking is likely to compound the effect of moderate preterm birth on pulmonary function,[45] and therefore smoking avoidance in this group should be encouraged. MLP infants are more likely to experience adverse sequelae from viral infections.[46,47] Subsequently, a lower threshold to seek medical care for respiratory symptoms may wish to be considered. Furthermore, mothers at high risk of preterm birth should be informed of the damaging effects that prenatal smoke and air pollutant exposure may have on postnatal pulmonary function.[48–50]

Given the potential long term consequences of MLP birth on respiratory health, it is essential to understand the economic and healthcare burden that rising rates of MLP birth may cause. A recent decision-analytic model estimated that for the first 18 years of life, a hypothetical birth cohort of 314,814 children - the number of total births in 2016 in Australia – a preterm birth rate of 8.5% will bear a cost of 1.413 billion Australian dollars, 39% of which is attributed to those born MLP.[7] A similar societal economic burden also exists within the US, where the current total incremental lifetime cost of an infant born MLP in 2016 is estimated to be 28,367 US dollars.[51] A 2016 MLP birth rate of 8.26% equated to 325,361 neonates being born MLP in the US.[52] Consequently, the incremental lifelong cost of this birth cohort is estimated to reach 9.2 billion US dollars.[51] In addition to lower expiratory airflows, emerging data suggest that MLP birth is associated with increased cardiometabolic risk and impaired neurodevelopment and social-emotional development compared with term birth.[53,54] Poorer outcomes across multiple health domains in conjunction with continued improvements in preterm birth survival rates is likely to lead to a further burden on healthcare systems. To address changes in the epidemiology of preterm birth alongside increasing preterm survival rates, high-quality studies investigating long-term health outcomes of preterm survivors are urgently required to inform government policy and clinical guidelines.[55]

This review provides an update and significant contribution to the current evidence base of the effect of MLP birth on later life expiratory airflows, with all studies eligible for meta-analysis having been conducted in the last decade. A major strength of our meta-analysis is that outcomes expressed as GLI z-score were obtained for all but one study, reducing a potential source of heterogeneity and making these results more relevant to current clinical practice. On the contrary, while all but one study reported worse expiratory airflows in those born MLP when compared with term-born controls, high levels of heterogeneity were observed in several of the analyses. Moreover, evidence of asymmetry due to heterogeneity was found when a funnel plot analysis and Egger's test were performed on studies that reported an FEV_1 z-score from participants born MLP.

Consequently, caution is advised when interpreting these findings. In addition, comparing to a population mean of 0 may have introduced bias given that poor GLI fit has been previously identified among several population groups.[56–58] We acknowledge that a limitation of our review is that we were unable to investigate longitudinal changes in expiratory airflows between MLP participants and term-born controls. Of the three studies with longitudinal outcomes, one used different reference equations at each time point,[37] while two studies reported z-scores derived from different reference equations.[14,15]

Due to a lack of longitudinal data, in conjunction with continuing improvements in neonatal care and reductions in the prevalence of smoking during pregnancy,[59] secular trends in the long-term pulmonary function of future MLP birth cohorts are difficult to determine. It remains unclear if MLP birth affects gas diffusion, static lung volume or lung clearance index. Future studies may wish to consider assessing pulmonary function measurements other than baseline spirometry to fully understand the effects of MLP birth on later life respiratory health. Finally, associations between perinatal and postnatal factors, such as early childhood respiratory illness, and pulmonary function later in life are poorly described in MLP cohorts. Further research is required to discern if reductions in later life pulmonary function are a result solely of preterm birth itself, or in conjunction with early life factors associated with MLP birth.

In conclusion, this study provides evidence that children and adults born MLP experience worse expiratory airflows than those born at term, although the reductions are small. While children and adults born MLP have more favourable long term respiratory outcomes than EP and VP survivors, general practitioners and pulmonary specialists should be aware that those born MLP may be at higher risk of COPD compared with term-born peers.

Contributors

CDB, CN, JLYC, TF, RM, SR, LWD, EJLEV and LW conceived and designed the study. CDB and CN performed the literature search. CDB, CN, JLYC, TF, RM, SR, LWD, EJLEV and LW were involved in data collection and interpretation. CDB, RM, and LW were involved in data analysis. CDB, CN, JLYC, TF, RM and LW were involved in data interpretation. CDB drafted the manuscript. All authors were involved in revising the manuscript and approved the final submitted version. CDB, CN and LW accessed and verified the underlying data reported in the manuscript.

Data sharing statement

All data used and generated in this study are available within the article and/or in the supplement material.

Declaration of interests

We declare no competing interests.

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Supplementary materials

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