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SYMPOSIUM

Consequences of Preterm Birth: Knowns, Unknowns, and Barriers to Advancing Cardiopulmonary Health

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Synopsis Preterm birth occurs in 10% of all live births and creates challenges to neonatal life, which persist into adulthood. Significant previous work has been undertaken to characterize and understand the respiratory and cardiovascular sequelae of preterm birth, which are present in adulthood, i.e., "late" outcomes. However, many gaps in knowledge are still present and there are several challenges that will make filling these gaps difficult. In this perspective we discuss the obstacles of studying adults born preterm, including (1) the need for invasive (direct) measures of physiologic function; (2) the need for multistate, multinational, and diverse cohorts; (3) lack of socialized medicine in the United States; (4) need for detailed and better-organized birth records; and (5) transfer of neonatal and pediatric knowledge to adult care physicians. We conclude with a discussion on the "future" of studying preterm birth in regards to what may happen to these individuals as they approach middle and older age and how the improvements in perinatal and postnatal care may be changing the phenotypes observed in adults born preterm on or after the year 2000.

Introduction

Very preterm birth, or birth occurring after less than 32 weeks of gestation, presents many challenges to health, function, and thus, life to the neonate that persist into adulthood (Thébaud et al. 2019). The World Health Organization developed various descriptors to describe the degree of prematurity such that "very" preterm birth is birth occurring 8-12 weeks early and "severe" preterm birth is birth occurring 12 or more weeks early. Specifically, impaired respiratory (Lovering et al. 2013, 2014; Duke et al. 2014, 2018; Molgat-Seon et al. 2019), cardiopulmonary (Goss et al. 2018; Laurie et al. 2018; Mulchrone et al. 2020), and cardiovascular (Lewandowski, Bradlow, et al. 2013; Huckstep et al. 2018, 2020) (Bates, Levy et al. 2020) function persists into adulthood, leading to an increased risk of early respiratory and cardiovascular diseases (Carr et al. 2017; Goss et al. 2018; Crump et al. 2019; 2020, 2021; Mulchrone et al. 2020).

Nearly 10% of the United States population is born preterm. Survival is dependent on gestational age, ranging from 76 to 90% in hospitals practicing active management, i.e., current treatment (Watkins et al. 2020). The high rate of preterm births ultimately translates to a large number of adults at higher risk of cardiorespiratory disease occurring earlier in life than those born at term. Despite the magnitude of the problem, the paucity of large data sets and substantial gaps in knowledge persist. Current challenges to advancing cardiopulmonary health in survivors of preterm birth include a need for larger, more heterogeneous cohorts, more direct (invasive) measurements, and a better understanding of how perinatal and neonatal treatment impact late respiratory, cardiopulmonary, and cardiovascular outcomes.

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In this perspective, we will briefly outline the known physiology and pathophysiology of adults born preterm and discuss what remains unknown. We will also discuss what is/will be needed to fill these gaps in knowledge and conclude with a discussion on the "future" of the study of adults born preterm as advances in medical care may, at some point soon, ameliorate the typical preterm born phenotype (i.e., impaired cardiopulmonary function).

Physiology of adults born preterm

As mentioned above, the study of adults born preterm, or rather the consequences of preterm birth that persist into adulthood, is an emerging area of study. Over the past decade, we have significantly furthered our understanding of the underlying physiology and pathophysiology of adults born preterm both at rest (Bates et al. 2014; Duke et al. 2022) and during exercise (Farrell et al. 2015; Barnard et al. 2020; Duke and Lovering 2020; Duke et al. 2022). Although many physiologic systems are impacted by preterm birth, we will focus specifically on the respiratory and cardiovascular systems. However, the interested reader is directed to a recent review that describes the impact of preterm birth on various organ systems in addition to the heart and lungs (Humberg et al. 2020). Below, we will briefly discuss and outline what is known in these areas.

Respiratory limitations and impairments.

Bronchopulmonary dysplasia is one of the most common sequelae of preterm birth, resulting in alveolar simplification, i.e., larger, but fewer, alveoli, and prolonged oxygen demand ("Prolonged oxygen demand" refers to whether or not the preterm infant received oxygen for 28 or more days post-birth) in the neonate (Thébaud et al. 2019). The anatomical changes to the preterm infant have been well-characterized (reviewed in [Kinsella et al. 2006]), particularly among infants that died in the perinatal period, have been well-documented, but less known about the development of the lung in survivors of preterm birth and how altered development may impact respiratory function.

Adults born preterm have impaired pulmonary function at rest compared to their age, sex, and height matched counterparts born at term (Mazloum et al. 2014; Bolton et al. 2015; Gibson et al. 2015; Islam et al. 2015; Davidson and Berkelhamer 2017; Raju et al. 2017; Malleske et al. 2018) with a pattern that is consistent with airflow obstruction, i.e., similar to a patient with mild chronic obstructive pulmonary disease. Expiratory airflow limitations can be the result of a combination of impairments, including lung size/volume, lesser driving (alveolar) pressure, and/or greater airway resistance. Previous work has demonstrated that adults born preterm have normal lung volumes (Halvorsen et al. 2004; Vrijlandt et al. 2006; Narang et al. 2009; Clemm et al. 2014; Duke et al. 2014, 2018, 2019; Lovering et al. 2014; Farrell et al. 2015; Caskey et al. 2016; Laurie et al. 2018; Molgat-Seon et al. 2019; Huckstep et al. 2020). Thus, smaller lungs do not appear to be an explanation for decreased respiratory function.

Driving (alveolar) pressure during a forced exhalation is a combination of expiratory muscle pressure generation (contraction) and elastic recoil of the lungs (Mead et al. 1967). To date, only one study has assessed respiratory muscle strength in individuals born preterm (10–12 years old) and found pressure generation to be normal (Jacob et al. 1998). However, this measurement needs to be made in adults born preterm to examine whether or not normal respiratory muscle strength extends into adulthood. Lung recoil pressure is a function of lung parenchyma elasticity, which can be reduced by emphysema or alveolar simplification. Lung recoil pressure has not been measured directly in adults born preterm, but can be done in awake, unanesthetized individuals (Gideon et al. 2020, 2021; Cross et al. 2021). Animal models of preterm birth suggest the presence of alveolar simplification, i.e., fewer but larger alveoli (Coalson et al. 1995; Bland et al. 2003; Dahl et al. 2018). However, work using computed tomography does not support the hypothesis that adults born preterm have alveolar simplification, i.e., a lesser lung recoil pressure (Margraf et al. 1991; Wong et al. 2008; Aukland et al. 2009; Caskey et al. 2016; Simpson et al. 2017). Thus, weak respiratory muscles and/or decreased lung elastic recoil do not appear to explain impaired pulmonary function at rest, leaving greater airflow resistance as the most likely explanation.

Plethysmographic and forced oscillation measures support greater airflow resistance as the largest contributor to impaired pulmonary function in individuals born preterm (Malmberg et al. 2002; Halvorsen et al. 2004; Vrijlandt et al. 2006, 2007; Udomittipong et al. 2008; Sarria et al. 2012). The physical factor that contributes greatest to airflow resistance is the diameter of the airways. Obtaining this measurement in humans is technically challenging and financially costly making it uncommon, but several imaging methods (computed tomography, optical coherence tomography, etc.) can quantify down to the 5th or 6th generation of the airway (Peters et al. 2021). Airway imaging techniques have yet to be employed in adults born preterm. However, we have previously utilized the dysanapsis ratio as an index for airway size (Duke et al. 2018). The dysanapsis ratio uses various spirometry-derived parameters to provide gross, indirect information about airway "size." Our

previous work suggests that adults born preterm have a smaller dysanapsis ratio (i.e., smaller airways) than individuals born at term with those born preterm who developed bronchopulmonary dysplasia having the smallest ratio (airways) (Duke et al. 2018). Measures of the relationship between lung structure and function, which uses volumetric capnography at fixed flow rates to define airway volume, at set lung volumes relative to functional residual capacity, can also be used as an index of airway resistance (Seymour et al. 2019). Future work should utilize complementary physiological and imaging techniques in humans or animals to better understand differences in tracheobronchial anatomy between term-born and preterm-born individuals.

The control of ventilation is also impaired in individuals that are born preterm. Katz-Salamon and colleagues first demonstrated that preterm infants have a blunted ventilatory response to hypoxia (Katz-Salamon et al. 1995; 1996). The blunted hypoxic ventilatory response persists into adulthood and may be the result of impaired carotid chemoreceptor development (Bates et al. 2014, 2018). The ventilatory response to hypercapnia appears to be heightened (Narang et al. 2022) and both pediatric and adults born preterm increased ventilation in response to exercise (Narang et al. 2022).

Cardiovascular limitations and impairments

Preterm-born individuals have cardiac and cardiovascular limitations/impairments that include significant cardiac remodeling, leading to functional and structural impairments in early life (Bates et al. 2020; Telles et al. 2020), that persist into adulthood (Bensley et al. 2010; Bertagnolli et al. 2018). This results in a thicker myocardium, despite no difference in total cardiac size. Thus, adults born preterm have smaller left and right ventricular volumes, leading to a reduction in myocardial functional reserve (Huckstep et al. 2018, 2020), during moderate-intensity exercise. At rest, individuals born preterm have mild cardiac dysfunction, including right ventricular systolic and left ventricular diastolic impairments (Lewandowski et al. 2013). Following exercise under hypoxic conditions, interstitial lung water is increased in survivors of prematurity, suggesting that subclinical diastolic dysfunction may lead to increased fluid filtration from the pulmonary capillary bed (Debevec et al. 2022). Left ventricular dysfunction may collaborate with increased airway resistance and altered ventilatory control to increase the total work of breathing, resulting in "cardiac output stealing" from the working muscles during exercise (Harms et al. 2000).

Adults born preterm may also have altered blood pressure and/or blood pressure control at rest and during exercise. Specifically, they have a greater diastolic blood pressure during exercise compared to normotensive individuals born at term (Huckstep et al. 2018). Using direct measures of arterial blood pressure, (Barnard et al. 2020) found greater systolic, diastolic, and pulse pressures during exercise. Diastolic pressure was attenuated by the addition of hypoxia, supporting the hypothesis that vascular reactivity is impaired. It has been suggested that altered autonomic function is the underlying cause of impaired blood pressure control and may cause the hypertensive phenotype observed in adults born preterm (Smith et al. 2005). More work is needed, but the current research suggests that individuals born preterm have reduced parasympathetic tone (Haraldsdottir et al. 2018). Given their cardiovascular impairments, adults born preterm are at a greater risk of cardiovascular diseases such as heart failure. A recent population study of 4.1 million persons found that heart failure incidence was greater in preterm-born (adjusted hazard ratio = 1.42; 95% confidence interval = 1.19–1.71) compared to term-born individuals (Crump et al. 2021).

What gaps in knowledge exist?

Despite the significant amount of work that has been done on adults born preterm, much is still unknown. As we have previously reviewed (Duke and Lovering 2020; Duke et al. 2022), there are a number of unknowns in this population. Our recent publication (Table 1; [Duke et al. 2022]), outlines much of what remains unknown in this population. In the respiratory system, work needs to be done to quantify the impact of preterm birth on static (lung/chest wall compliance) and dynamic (work/power of breathing) respiratory mechanics, respiratory muscle function, airway responsiveness and function, and dimensions of breathlessness (if present). One unique and emerging means of further challenging the underdeveloped cardiopulmonary system of adults born preterm is the use of environmental stressors, i.e., hypoxia, heat stress, etc. A recently published viewpoint outlines this interesting approach to studying adults born preterm (Debevec et al. 2022). In the cardiopulmonary systems, we need more work with direct measures of pulmonary pressure and resistance, direct measures of left atrial pressure, and work quantifying pulmonary gas exchange efficiency in those with severe preterm birth and severe bronchopulmonary dysplasia. Finally, in the cardiovascular system, we need direct measures of cardiac output, cardiac pressures, and myocardial functional reserve.

As can be discerned from the above, the greatest need(s) is/are for work to be undertaken using direct (i.e., invasive) measurements of physiologic func-

Table 1 Details obtained from medical records in adults born preterm from a previously published cohort.

	O_2 duration	O_2 maximum	Ventilator?	CPAP?	PDA?	Steroids, P?	Steroids, A?	Surfactant?	BPD?
1	65	80	Yes	Yes	Indomethacin	?	?	yes	Old
2	97	50	Yes	Yes	Indomethacin	?	?	yes	Old
3	~75	56	Yes	?	PDA no tx	Betameth	Decadron	?	Old
4	>180	45	Yes	Yes	No PDA?	?	Decadron	yes	New, mild
5	59	40	Yes	?	Ligation	?	?	no	Old
6	34	70	Yes	No	Small PDA	?	?	?	Old
7	>180	100	Yes	Yes	?	?	Pred (asthma)	?	Old, severe
8	>47	100	Yes	Yes	Ligation	?	?	Exosurf study	Old
9	>47	100	Yes	Yes	Ligation	?	?	Exosurf study	Old
10	32	28	Yes	Yes	no PDA	Betameth	?	yes	Old, mild
11	150	?	?	?	Indomethacin	?	?	?	Old, moderate
12	144	?	Yes	No	Ligation	?	?	?	Old, moderate
13	>270	100	Yes	No	No PDA	No	Decadron, Pred	Exosurf study	Old, severe
14	36	70	No	Yes	?	?	?	?	New, mild
15	>120	100	Yes	No	Ligation	No	No	Yes	Old, moderate
16	>78	100	yes	?	No PDA	?	?	?	?
17	32	?	yes	Yes	Indomethacin	yes	yes	yes	New, mild
18	>127	100	Yes	?	Indomethacin	Yes	Yes	Yes	New, moderate
19	29	60	Yes	No	No	Yes	No	No	New, mild
20	22	100	Yes	No	No	No	No	Ua	No
21	2	Blow-by	Yes	No	No	No	No	Ua	No
22	1	40	No	No	No	Yes	No	no	No
24	5	?	Yes	No	No	No	No	Ua	No
25	7	30	Yes/Yes	No	No	Yes	No	Ua,Cen	No
26	7	25	Yes	Yes	No	No	No	Ua,Uv	No
27	4	30	Yes/Yes	Yes	Indomethacin	Yes	Yes	Ua,Uv,Cen	No, Deca → RmAir
28	1	30	Yes	No	No	Prob No	No	?	No, but asthma later
29	21	30	Yes	No	Ligation	Prob No	No	Uv,Cen	No
30	7	30	Yes	No	No	No	No	Ua	No
31	0	21	No	?	no records	?	?	?	?
32	9	30	Yes	Yes	Indomethacin	Yes	No	Ua,Uv,Cen	No
33	7	26	Yes	No	No	Yes	No	Ua	No
34	1	Blow-by	Yes/Yes	Yes	No	Yes	No	Ua,Uv	No
35	8	74	Yes/Yes	Yes	Indomethacin	Prob no	No	Ua	No

O_2 duration refers to number of days receiving oxygen therapy; O_2 maximum refers to the highest % oxygen received; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus; indomethacin is a non-steroid anti-inflammatory provided to aid in PDA closure; ligation is a surgical procedure to close the PDA; Steroids, P, steroids given perinatally; Steroids, A, steroids given antenatally; betameth, betamethasone is a steroid medication; decradron, is a steroid medication, Pred, prenisone is a corticosteroid medication; Exosurf study, a controlled clinical trial for use of exogenous surfactant; BPD, bronchopulmonary dysplasia, which can be categorized as "old" or "new" depending upon whether or not exogenous surfactant treatment was used.

tion. In doing so, we will be able to further our understanding in a variety of aspects of physiologic function, but also identify mechanisms to target and improve function in adults born preterm and provide guidance to clinicians in assessing sources of cardiopulmonary disease risk. One additional, general, need is for the above-mentioned work to be done in large cohorts. Some direct, invasive measures have been undertaken in adults born preterm (Lovering et al. 2013; Duke et al. 2014; Farrell et al. 2015; Goss et al. 2018; Mulchrone et

al. 2020), but the cohorts were small and likely skewed to the most healthy and physically able of the population. Accordingly, two important questions that must be posed when considering *how* to fill these knowledge gaps is, *can* we fill these knowledge gaps and, if so, *how*.

We also do not know how secondary co-morbidities impact cardiopulmonary disease risk and outcomes in survivors of prematurity. For example, individuals with Down syndrome are at increased risk of being premature and small for gestational age birth. We recently reported that overall cardiovascular disease risk in adulthood is higher in these individuals, and that many of the sex differences seen in the general population are not present in individuals with Down syndrome (Bates et al. 2023). We do not know the degree to which prematurity contributes to this risk. Preterm birth also increases the risk of myeloid leukemia and some solid tumors that are often treated with cardiotoxic chemotherapy (Seppälä et al. 2021). We do not know whether preterm birth increases the risk of chemotherapy-induced heart failure and we do not know the impact COVID-19 has had on their cardiopulmonary health (Bates 2021). We have little information about the impact of race, sex, and gender (Bates and Haack 2020) to cardiopulmonary outcomes in prematurity. Future studies should extend beyond functional assessment in seemingly healthy individuals to include diverse populations and intersections with potential contributors to heightened risk.

What is needed to fill these gaps and is it possible?

There are several aspects of preterm birth, specifically in the United States, that may make filling these knowledge gaps extremely difficult, if not impossible. First, the need for direct (invasive) measures is of critical importance. Attaining these data in a sufficiently large cohort is critical for generalizability and this can be technologically challenging and expensive. Invasive studies require active participation from specialized clinicians that are already overburdened by clinical job duties (Klick et al. 2023). Second, organizations including the American Heart Association and National Institutes of Health need to support the development and maintenance of large, multistate cohorts that are racially and geographically diverse so that we can better define the prenatal, perinatal, and lifelong contributors to increased respiratory and cardiovascular disease risk, including preterm birth. Third, the lack of socialized medicine and a centralized medical records system in the United States impairs the ability to obtain longitudinal data required for generalizability of findings from a cohort. Fourth, medical care is complex and dynamic, and standard of care of the neonate change routinely. Individuals born today likely have a different physiology than individuals born 30 years ago. Finally, given that medicine in the United States is not regulated at the federal government level and there are no current position documents on cardiopulmonary risk in the preterm population, knowledge of preterm birth-related outcomes are routinely lost during the transition from pediatrician to adult primary care physician. Here, we will consider these aspects in more detail.

Cohort willing to undergo regular invasive studies?

As discussed above, there is significant need for direct measurements to be made in adults born preterm. Previous investigators have made invasive measures of pulmonary gas exchange efficiency via arterial catheterization (Lovering et al. 2013; Duke et al. 2014; Farrell et al. 2015) and of pulmonary hemodynamics via right heart catheterization (Goss et al. 2018; Mulchrone et al. 2020). Collectively, in the gas exchange studies, a total of $n = 24$ adults born preterm ($n = 12$ with bronchopulmonary dysplasia) were studied and in the studies of pulmonary hemodynamics only $n = 11$ adults born preterm were measured. Importantly, these sample sizes are likely too small to generalize findings to the entire population of adults born preterm.

It is important to consider the limitations associated with invasive measurements. Because of the risks associated with invasive procedures these cohorts likely skew to healthier adults born preterm that do not have overt sequelae or heightened cardiopulmonary risk (Lovering et al. 2013; Duke et al. 2014). Second, supplies, clinical resources, physician oversight, etc. can make the cost of invasive studies necessarily high or, frankly, impossible as academic physicians' clinical workloads increase in the face of changing healthcare economics. Nonetheless, the need for larger cohorts in studies with gold standard physiological measures is great.

One could argue that it is unethical to expose more individuals to the risk of invasive measures than is needed to be adequately powered, statistically. This is a more than reasonable point; thus, perhaps it is not about the *size* of this cohort, but rather the diversity (race, ethnicity, and geographically) that is more important? Perhaps what is really needed is several groups across the country, working together and making identical measurements, to enhance generalizability of findings. This seems to be an issue of priority rather than feasibility as other groups, including burn victims, pediatric cancer patients, have nationwide networks (Lee et al. 2022; Watso et al. 2022), and the National Institutes of Health maintain

an additional 79 patient-centered registries (searched March, 2023 https://www.nih.gov/health-information/nih-clinical-research-trials-you/list-registries).

Development of multistate cohorts?

A continuation of the above section, is the need to develop multistate cohorts of individuals born preterm. In the United States there exist several geographically-limited preterm birth cohorts that have been followed/tested serially with detailed neonatal records, including the Newborn Lung Project at the University of Wisconsin and The Tiniest Babies Registry at the University of Iowa. These cohorts (and serial measurements) are critical in expanding our understanding of the sequelae associated with preterm birth, as well as how their physiology changes as they age from infancy to adolescence to adulthood and beyond. However, individuals including in these cohorts are often born in the same geographic region or even in the same hospital. Additionally, oftentimes these cohorts are assembled at premier medical and research institutions meaning the preterm infants are being provided the most up-to-date and cutting-edge treatment available. Thus, these infants are likely to have better overall survival and fewer overt sequelae. A consortium of cohorts that agrees on measurements, and shared outcome data, would improve the socioeconomic and racial diversity of datasets, allow for the identification of differences in care between centers, and is aligned with the National Institutes of Health's requirements for active data sharing.

One idea may be to build multistate cohorts of individuals born preterm, which could be done by having large medical centers across the country enroll individuals they have seen or treated. Building a cohort in this regard has many challenges, including having multiple groups engaged and responsible for maintenance of the cohort. This arrangement would bring about some challenges, but the quality and productivity of remote work and collaboration has increased dramatically since 2020. The Neonatal Hemodynamics Research Centre has made efforts over the past decade to both standardize the delivery of care internationally, and to create cohorts centered around research questions in the neonatal intensive care unit (https://neonatalhemodynamics.com/). They serve as an outstanding model of building cohorts with follow-up beyond the perinatal period.

Other countries, including Sweden and Australia, have built nationwide cohorts, but are much smaller countries than the United States. Thus, the United States will face challenges that may have not been encountered by others. Another challenge will be that multiple groups are going to be making the same exact measurement in their respective sub-cohorts. Many standard measurements of interest, i.e., spirometry, are highly standardized with procedures and interpretations spelled out in Society statements. However, other measurements, i.e., respiratory system compliance, are not standardized and so training of multiple individuals at multiple sites would bring about some logistical difficulties. Finally, the greatest challenge may be keeping track of all of the individuals enrolled/engaged in the cohort. Cardiopulmonary-focused projects like COPDGene and the Framingham Heart Study are valuable models for how to perform this sort of work in a longitudinal preterm cohort (Taylor et al. 2023; Verstraete et al. 2023). External advisory boards with collaborators from cohort studies with similar design would be valued advisors.

Despite the above-mentioned difficulties and challenges, there are some obvious positives that would result from building a cohort like this. First and foremost, building this kind of cohort would increase the potential number of individuals enrolled. Likewise, the cohort would increase, substantially, in diversity. There would, presumably, be more diversity in terms of race and ethnicity, but also in socioeconomic status and geography. Combining data from cohorts from different geographic regions would help to wash out any location or hospital specific treatments or effects. Finally, by having multiple measurement locations, it may increase long-term participation in research. Instead of an individual having to fly from southern California back to Wisconsin for measurements, they can visit the regional site in or much nearer to the area they are living in. It will be this system that will ultimately result in studies on "older" individuals (i.e., 55 + years) born preterm.

Lack of socialized medicine in the US

The healthcare insurance space is a combination of government sponsored coverage (i.e., Medicare/Medicaid), coverage from private insurers with employers paying some or all of the monthly premiums, self-coverage, and lack of insurance. Patient treatment is influenced by the goals of care set by the physician and patient, the options that a group or hospital are willing or able to provide, what is allowable under state and federal law, and what an insurer is willing to cover. These influences all lead to potentially highly heterogenous care.

One issue specific to the perinatal period is linking specific differences in neonatal care, i.e., antenatal or neonatal steroids, ventilator settings, etc. to pediatric and adult outcomes associated with preterm birth. For example, suppose that two infants are born after 29 weeks of completed gestation, are the same sex, and approximately the same mass at birth. One infant is treated

with a "cocktail" of three steroids while the other is provided only two of those same steroids. The latter infant, has better pediatric and adult outcomes. Is this due to not receiving the third steroid or something else entirely? The ability to answer this question is further confounded by the fact that the information contained in birth/medical records is not standardized and medical treatment across the lifespan is highly variable.

A second issue is that treatment is not standardized across the country. Importantly, it is difficult to call this an issue as patients should be treated as the unique individual's they are rather than as the condition they may have. However, the variable and non-standardized treatment and care for individuals born preterm makes the population very heterogeneous. Obviously, the value of an animal model is that one can provide identical insult and treatment, which enhances the quality of inferences drawn from a series of experiments. The discussion, though, is cyclical because an animal model provides maximum control over insult and treatment, but does it appropriately mimic the human population? Nonetheless, having a cohort of very similarly treated individuals born preterm would provide insightful findings.

A third issue resulting from the lack of socialized medicine in the United States is that information contained in birth/medical records is not standardized (see below for more discussion). This makes extraction of information on treatments, etc. a very arduous task that sometimes cannot be completed, i.e., it is unclear whether an individual received a particular drug or not. Having a more standardized form for birth records, particularly for those born preterm or have an otherwise complicated birth, would be immensely helpful, but probably not feasible given the many software and recording keeping options available. Perhaps a feasible first step would be a pubic registry where preterm born individuals, or their parents, can enroll themselves and provide any information regarding their care and treatment throughout their life.

Detailed, organized, and high-fidelity birth record cohorts

One common issue that we have encountered is trying to discern specific details in medical/birth records about neonatal care. In general, it is easy to discern gestational age, weight, and length at birth, but things can be difficult beyond this. Table 1 displays information extracted from birth records in a cohort of adults born preterm in Oregon. Note the many question marks on areas where it could not be determined whether or not an infant received a particular drug/treatment/therapy. Likewise, it is not always apparent for how long these drugs/treatments were provided.

Knowing the precise duration and fraction of oxygen therapy provided during the neonatal period is challenging. The presence and severity of bronchopulmonary dysplasia can be defined by the duration of mechanical ventilation and oxygen therapy, as well as the %/fraction of oxygen being delivered to the infant (Jobe and Bancalari 2001). Therefore, failure to discern detailed information about these treatments prevents accurate classification of an infant. One challenge is also that mechanical ventilation and/or oxygen therapy is not always continuous as the neonatologist is trying to ween the infant off both as early as possible. Thus, sometimes an infant may receive oxygen for some number of days, come off, and then be put back on. This adds an opportunity for details to be inadvertently left off. The University of Iowa and Baylor College of Medicine have addressed similar problems with the implementation of the SickBay program (Elizondo et al. 2019). SickBay provides high frequency recording of the clinical monitors in the Neonatal Intensive Care Unit, like what LabChart has provided to physiologists. Having a group of centers willing to participate in this sort of program and share data would allow for the first machine learning applications to long-term neonatal outcomes research.

Transfer of knowledge/information from pediatrician to adult physician?

One of the biggest challenges for the treatment of adults born preterm is that, frequently, medical information is not transferred from pediatrician to primary care physician or adult pulmonologist. To make things more difficult, hospitals often destroy medical records after 3–7 years (for issues related to data storage space and privacy) so the birth records are often not available. Thus, information from birth is often lost for good if not transferred from physician to physician or kept by the patient (or their parents).

We recently surveyed the major Midwest and Big10 medical centers and asked the question "Do General, Family, and Internal Medicine practitioners at your institution ask about birth history." All the applicants replied "no" (Bates et al. 2018). This severely limits our ability to link birth history to early life events. Given the size of this population and their enhanced cardiovascular risk, we could substantially move the needle by adding basic questions about birth history to overall cardiovascular risk questionnaires. The TriNetX platform has improved our ability to ask questions about large numbers of patients that were not previously able to be collated locally (Bates et al. 2023),

but requires appropriate documentation of the medical record with ICD-10 codes. Currently, birth history is a restricted search field. If the 78 current members of the TriNetX program agreed to asked about birth history, we could immediately generate a large dataset that would be incredibly valuable to preterm birth outcomes researchers.

Additionally, individuals often move away from "home" and become a patient of a primary care physician or specialist in an area not near where they grew up. Depending upon the patient's level of knowledge and interest in their health, they may not disclose, i.e., they do not know or do not realize it may matter, that they were born preterm. Do adult physicians know to ask about this? Do they view this as an important indicator of their new patient's health and longevity? As discussed above, there are several important late consequences of preterm birth, which may result in an increased risk of developing lung and/or heart disease later in life. Therefore, this is a question that every adult physician should ask. Likewise, moving away from "home" means that the familiarity a physician has with a patient from treating them or their parents is lost, as is the knowledge of their birth status.

Future outcomes of preterm birth—advances in medicine and aging

The last question that needs to be considered in regards to the study of adults born preterm is, *what is the future of this area of research?* Specifically, this question asks if an individual born 10 weeks preterm in 1980 "looks like" an individual born preterm in 2000? Second, what happens to adults born preterm as they reach their 40's, 50's, 60's, and beyond?

Based upon the spirometry data in cohorts of adults born preterm in the 1980–90s compared with more recent cohorts (born late 1990s and early 2000's) the answer to the second question is "no." It is very clear that the perinatal and postnatal medicine has advanced substantially since bronchopulmonary dysplasia first appeared in the scientific literature in 1967 (Northway and Rosan 1967). In Fig. 1 we have plotted important spirometry data (forced expired volume in 1 s [1A] and forced expiratory flow from 25 to 75% of vital capacity [1B], as a % of predicted) as a function of birth year in various cohorts that we have studied over the last 10–12 years. Note that the term born cohorts in both figures are centered on the 100% of predicted lines, but there is substantial spread for the preterm born cohorts with some falling below the 100% of predicted line, as expected. Importantly, in the preterm born individuals born near or after 2000, the spread is narrower and more individuals are falling at or above the 100% of predicted line. This suggests that the adults born preterm who were born more recently have a phenotype with pulmonary function that is better than the older cohorts. Vollsaeter et al. (2015) have demonstrated similar findings in their cohorts of Norwegian children born preterm around 1990 and 2000.

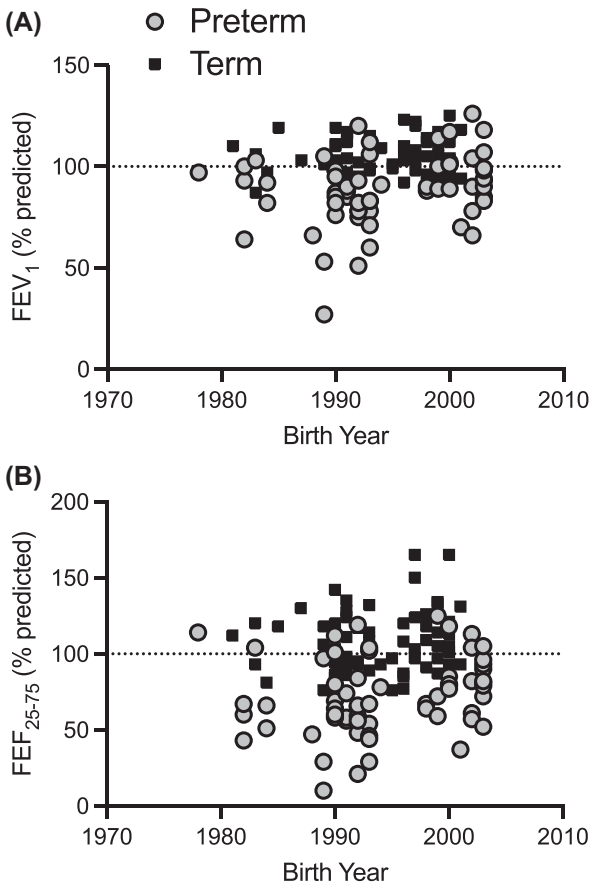

Fig. 1 Spirometry in adulthood as a function of year born. (A) Forced expired volume in 1 s against birth year in term born (black square) and preterm born (gray circle) adults. (B) Forced expiratory airflow from 25 to 75% of vital capacity against birth year in term born (black square) and preterm born (gray circle) adults. In both panels, note that pulmonary function is better in those adults born preterm who were born closer to the year 2000.

An important area of future exploration in the population of adults born preterm is to better understand "how" they will age. Pulmonary function and aerobic exercise capacity are known to peak around the third decade of life and then decline thereafter. In healthy individuals free of respiratory and/or cardiovascular disease, pulmonary function may never decline to a disabling level. However, it is not known whether or not this is true in adults born preterm who may have a lifetime peak of pulmonary function that is 20–25% lower than their counterparts born at term (Duke et al. 2022). The primary reason that this is not known

is because the population of adults born preterm who are >50 years old is too small. Thus, an important, and necessary, are of future study is to better understand how pulmonary function and aerobic exercise capacity change with age in adults born preterm compared to those born at term.

Conclusions

Adults born preterm have lesser respiratory and cardiovascular function at rest, but many gaps in knowledge remain. To address these knowledge gaps, large, multistate cohorts need to be assembled and direct measures of various aspects of physiologic function are needed. However, many challenges are present that may make filling these gaps in knowledge very difficult. These challenges include, but are not limited to, need for a cohort willing to have serial, invasive measures performed, lack of socialized medicine in the United States, the need for more detailed birth/medical records, and a transfer of information from pediatrician to adult physician. Finally, the future of research in adults born preterm will be interesting as perinatal and neonatal medicine continue to improve and lessen the sequelae associated with preterm birth in the United States.

Author contributions

C.D.H., M.L.B., A.T.L., and J.W.D. drafted the manuscript. All authors approved the final version of the manuscript and take responsibility for the integrity of the data and accuracy of the data analysis.

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Conflict of Interest

The authors have no conflict of interest to report.

Data Availability

Raw data presented in this manuscript are available upon reasonable request to the corresponding authors.

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