Changes in the Preterm Heart From Birth to Young Adulthood: A Meta-analysis

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abstract

CONTEXT: Preterm birth is associated with incident heart failure in children and young adults.

OBJECTIVE: To determine the effect size of preterm birth on cardiac remodeling from birth to young adulthood.

DATA SOURCES: Data sources include Medline, Embase, Scopus, Cochrane databases, and clinical trial registries (inception to March 25, 2020).

STUDY SELECTION: Studies in which cardiac phenotype was compared between preterm individuals born at <37 weeks’ gestation and age-matched term controls were included.

DATA EXTRACTION: Random-effects models were used to calculate weighted mean differences with corresponding 95% confidence intervals.

RESULTS: Thirty-two observational studies were included (preterm = 1471; term = 1665). All measures of left ventricular (LV) and right ventricular (RV) systolic function were lower in preterm neonates, including LV ejection fraction (P = .01). Preterm LV ejection fraction was similar from infancy, although LV stroke volume index was lower in young adulthood. Preterm LV peak early diastolic tissue velocity was lower throughout development, although preterm diastolic function worsened with higher estimated filling pressures from infancy. RV longitudinal strain was lower in preterm-born individuals of all ages, proportional to the degree of prematurity (R² = 0.64; P = .002). Preterm-born individuals had persistently smaller LV internal dimensions, lower indexed LV end-diastolic volume in young adulthood, and an increase in indexed LV mass, compared with controls, of 0.71 g/m² per year from childhood (P = .007).

LIMITATIONS: The influence of preterm-related complications on cardiac phenotype could not be fully explored.

CONCLUSIONS: Preterm-born individuals have morphologic and functional cardiac impairments across developmental stages. These changes may make the preterm heart more vulnerable to secondary insults, potentially underlying their increased risk of early heart failure.

The incidence of preterm birth is increasing and already affects >10% of live births worldwide.\(^1,^2\) Gestational age at birth has a strong inverse association with cardiovascular mortality in young adulthood.\(^3\) Furthermore, population-based studies have demonstrated that preterm birth is a newly recognized risk factor for early heart failure and ischemic heart disease in young adulthood.\(^4,^5\) Observational studies revealing impaired left ventricular (LV) systolic reserve with pump failure under physiologic stress,\(^6\) right ventricular (RV) dysfunction,\(^7,^8\) and distinct ventricular morphology\(^9\) may help explain this increased risk. Nevertheless, there remains variability in published results, predominantly from small-sized cohorts, as well as insufficient characterization at different developmental stages. This hinders the identification of amenable targets and appropriate developmental windows for the adoption of primary prevention strategies.

We therefore performed a systematic review and meta-analysis, combining case-control published records from inception to March 25, 2020, with the aim to determine a more accurate effect size of prematurity on cardiac remodeling across developmental stages from birth to young adulthood. We hypothesized that many of the cardiac differences between preterm- and term-born individuals would emerge during infancy and persist during childhood and into young adulthood.

**METHODS**

The meta-analysis design, performance, and reporting were made in accordance to MOOSE (Meta-analysis of Observational Studies in Epidemiology) group guidelines.\(^10\) The protocol was registered with PROSPERO International Prospective Register of Systematic Reviews (identifier CRD42016038650).

**Data Sources and Searches**

Search strategies were developed by a medical librarian (L.Y.) for the concepts of cardiac function, performance, and measures; echocardiography; cardiovascular magnetic resonance; and preterm- and term-born individuals. Search hedges combining standardized terms and key words were implemented in Embase (1947 to present), Ovid Medline (1946 to present), Scopus (1823 to present), Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov (2000 to present) (Supplemental Information). Authors’ data records and bibliographies were also screened. No language or date restrictions were applied. First and last authors of included studies published from 2000 to present and first and last authors of relevant conference abstracts published in the preceding 24 months were contacted. This resulted in the retrieval of unpublished data from 12 publications.\(^11–22\) In addition, patient-level data and unpublished parameters were available from analyses of 692 individuals (cases = 302; controls = 390) from an additional 5 publications.\(^6,^7,^9,^23,^24\)

**Selection of Studies**

Searches were completed on March 25, 2020, resulting in 3057 citations after removal of duplicates, which were independently reviewed by 2 authors (F.T. and N.M.). Inclusion criteria were as follows: (1) concurrent evaluation of preterm-born cases (≤37 weeks’ gestation) and term-born controls (≥37 weeks’ gestation), (2) reported relevant cardiac structure and/or function, and (3) evaluation performed after birth. For cases to represent individuals without significant neonatal and infant morbidity, studies were excluded by the presence of (1) cardiac malformation, (2) acute illness, or (3) specific stratification by intrauterine growth restriction (IUGR), small for gestational age (SGA), bronchopulmonary dysplasia (BPD), or patent ductus arteriosus. Results from these studies, with the exclusion of BPD, IUGR, SGA, and patent ductus arteriosus, for preterm infants were used when available.

**Data Extraction and Outcome Measures**

Data were extracted into a customized database containing predefined measures of LV and RV structure, systolic function, and diastolic function based on recommendations by the American Society of Echocardiography, European Association of Echocardiography, and Society of Cardiovascular Magnetic Resonance guidelines (Supplemental Information).\(^25–28\) Results were stratified by developmental ages: (1) neonates <28 days, (2) infants ≥28 days to ≤1 year, (3) children >1 to ≤14 years, (4) adolescents >14 to <18 years, and (5) young adults ≥18 to 35 years.

Primary and secondary LV and RV outcomes were determined on the basis of clinical utility and validity of the measures.\(^25–28\) LV primary outcomes were as follows: LV ejection fraction (LVEF), LV longitudinal strain, LV peak systolic tissue velocity (LV’s’) (mitral valve annulus) and LV peak early diastolic tissue velocity (L’v) (mitral valve annulus), LV early Doppler inflow velocity/peak early diastolic tissue velocity ratio (E/E’) (estimated filling pressures), LV Doppler early/late diastolic mitral inflow velocity ratio (E/A), LV end-diasstolic volume indexed to body surface area (LVEDVI), LV stroke volume indexed to body surface area (LVSVI), and LV mass indexed to body surface area (LVMII). RV primary outcomes were as follows: RV longitudinal strain and RV peak systolic tissue velocity (Rv’s’) (tricuspid valve annulus). Secondary outcomes were as follows: RV peak early diastolic tissue velocity (Rv’s’) (tricuspid valve annulus), mitral
Developmental Stage and Gestational Age Stratification

In addition to result stratification by developmental ages, pooled analyses of cardiac function in children and young adults were performed, as appropriate, to elucidate potential contributors to their increased heart failure risk. Stratification at each developmental stage according to the degree of prematurity was made when sufficient data were available, with the cutoff of <32 weeks’ gestation selected on the basis of heart failure risk stratification.

Statistical Methods

Meta-analyses were performed by using Review Manager version 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Nonstandardized mean differences were weighted by the inverse variance and pooled by using random-effects models to estimate the weighted mean differences (WMDs). WMDs have also been expressed as percentages of age-based normal data derived from the weighted pooled mean for term-born individuals (percentage weighted mean difference [%WMD]). For instance, if the weighted pooled mean for term-born individuals for a given measure was 10 and the WMD was 2, then the %WMD would be 20%. The χ² test of homogeneity (Cochran Q test; P < .1) and I² statistic (>|50|) were calculated to assess statistical significance and the degree of heterogeneity, respectively. On the basis of thresholds defined in the Cochrane Handbook of Systematic Reviews, studies with I² <30% were considered to have low heterogeneity, whereas those >75% were considered to have high heterogeneity. We planned to evaluate publication bias visually with funnel plots and statistically with the test from Egger et al for pooled analyses containing ≥10 studies; however, because only 1 of the pooled analyses reached that threshold, supplemental publication bias testing was done for analyses containing ≥3 studies (Supplemental Figs 21–26). Forest plots were depicted for visual interpretation of the individual study-specific and pooled estimates with respective 95% confidence intervals (CIs).

Although some of the variation across studies may be due to methodologic diversity, it may also be due to differences in the characteristics of the study populations. Random-effects meta-regressions were therefore completed with Wilson’s SPSS macro by using IBM SPSS Statistics version 25 (IBM SPSS Statistics, IBM Corporation) to determine which covariates or study-level factors drive the measures of effect. In models, the influence of gestational age and birth weight was primarily explored and, secondarily, the influence of age, sex, IUGR or SGA, and BPD.

Quality Assessment

Quality assessment was performed independently by 2 authors (F.T. and N.M.) using a modified score system specific to preterm health for quality assessment of observational studies selecting according to study design, matching of cases and controls, preterm group stratification, incidence of IUGR or SGA and BPD, completeness of participant demographics, cohort size, blinding of assessors, and reproducibility of reported results. A scale points system from 0 to 2 for each parameter was summed and adjusted to a percentage score, with high or moderate quality assigned to studies with a score >65% or 50%, respectively (Supplemental Table 1). Overall quality scores for meta-analyses were calculated as the sum of individual study quality scores weighted according to random-effects inverse variance.

RESULTS

Systematic review yielded 38 eligible publications of 32 unique observational studies comprising 3136 individuals (Fig 1) (preterm = 1471; term = 1665). All 38 of the included eligible publications were in English. Of these, 21 records revealed data in neonates (n = 1709; preterm = 742) and infants (n = 940; preterm = 446); 7, in children (n = 635; preterm = 348; mean ages: 6.7–11 years) and, in adolescents; and 6, in young adults (n = 582; preterm = 301; mean ages: 18–25.1 years). All but 1 study provided analyses by echocardiography. A decision to include this cardiovascular magnetic resonance study was based on high-quality assessment and impact to the study field.

Demographic characteristics for each study are presented in Supplemental Table 2. Cases and controls were matched for age in all studies. Cases with IUGR or SGA were completely excluded in 13 studies and unreported in 11 studies, whereas cases with BPD were excluded in 5 studies and unreported in 9 studies. The overall reported incidence of IUGR or SGA and BPD was low (<15%) in 63% and 66% of studies, respectively, and high (30–50%) in 22% and 28% of studies, respectively. Two studies were excluded because of 100% IUGR or BPD stratification, and 2 studies were
excluded because of >50% IUGR or SGA incidence together with a low-quality assessment secondary to pilot methodology and low cohort size ($n = 30$ and $25$; cases = $15$ and $13$; controls = $15$ and $12$, respectively), unfavorable retrospective recruitment design, and very low birth weight preterm stratification.\textsuperscript{55,56}
As shown in Supplemental Table 3, meta-analyses were not possible at all developmental stages for all parameters. For instance, sufficient data for analyses of RVs’ and RVEs, as well as TAPSE and MAPSE, were only available for neonates; LVSVI analysis was only possible in children and young adults; and analyses of LV length and LVEDVI could only be done for young adults. Because researchers of only 6 studies investigated individuals born preterm at ≥32 mean weeks’ gestation in infancy,13,21,23,30,39,41 none in childhood, and only 1 in young adulthood,6 analyses stratified to ≥32 weeks’ gestation were only possible for E/A, LVFS, LVMI, and LVPWd in infants and were not possible in children or young adults. Participants-level values were used to stratify data from 3 studies6,13,23 for <32 and ≥32 weeks’ gestation subanalyses. Summaries for primary outcomes are presented in Table 1, and summaries for secondary outcomes are presented in Supplemental Table 4.

Global Cardiac Impairment in Preterm Neonates

As seen in Table 1 and Supplemental Table 4, all measures of LV and RV systolic function were lower in preterm versus term neonates, including LVEF (Fig 2) (WMD −2.89%; 95% CI −5.18 to −0.61; %WMD = −4.5%; P = .01). The preterm impairment in comparison with term neonates was greater (χ² = 26.40; P < .001) for the RV measure TAPSE (WMD −2.29; 95% CI −2.81 to −1.77; %WMD = −26.3%; P < .001) than the corresponding LV measure MAPSE (WMD −0.87; 95% CI −1.03 to −0.71; %WMD = −15%; P < .001).

Biventricular diastolic function, measured by LVe’ and RVe’, was also lower in preterm neonates compared with term neonates (Fig 3) (LVe’: WMD = −1.19 cm/second; 95% CI −1.76 to −0.62; %WMD = −18.6%; P < .001; RVe’: WMD = −2.08 cm/

second, 95% CI −2.43 to −1.73; %WMD = −29.7%; P < .001). Preterm neonates showed lower LV E/A, although there were no significant differences in LV E/e’.

Stratification of the preterm neonatal cohorts according to gestational age reduced the heterogeneity of analyses and revealed that preterm deficits were larger in those born at <32 weeks’ gestation than those born at ≥32 weeks’ gestation for all parameters except LVEF. In comparison with controls, LVs’ was twofold lower (χ² = 5.05; P = .02) in preterm neonates born at <32 weeks’ gestation (WMD −0.93 cm/second; 95% CI −1.15 to −0.71; %WMD = −21.1%; P < .001) than those born at ≥32 weeks’ gestation (WMD −0.45 cm/second; 95% CI −0.80 to −0.09; %WMD = −10.5%; P = .01). Elevated E/e’ was only evident in preterm neonates born at <32 weeks’ gestation (WMD 1.73; 95% CI 0.96 to 2.50; %WMD = 20.1%; P < .001).

Evolution of LV Systolic Function

In infancy, LVEF and LVs’ were similar between preterm and term individuals, although longitudinal systolic strain (WMD 1.55%; 95% CI 0.89 to 2.21; %WMD = −7.1%; P < .001) and LVFS (WMD −1.11%; 95% CI −2.18 to −0.04; %WMD = −3.3%; P = .04) were inferior in preterm infants. LVFS and LVs were similar in childhood, but they revealed nonsignificant trends of higher preterm function in young adulthood, which reached statistical significance for LVEF in pooled analysis of children and young adults (WMD 2.11%; 95% CI 0.02 to 4.15; %WMD = 12.9%; P = .02). Children and young adults (WMD 2.73%; 95% CI 0.89 to 4.57; %WMD = −10.6%; P = .004), and pooled data for children and young adults (WMD 3.02%; 95% CI 2.23 to 3.82; %WMD = −14.3%; P < .001). Because of insufficient numbers, data from Aye et al23 were excluded for RV strain stratification of preterm neonates and infants <32 weeks’ gestation. Stratification for those born at <32 weeks’ gestation resulted in greater differences compared with term controls (neonates: WMD 3.87%; 95% CI 1.54 to 6.20; %WMD = −16.2%; P = .001; infants: WMD 3.01%; 95% CI 0.81 to 5.22; %WMD = −11.7%; P = .007).

Evolution of LV Diastolic Function

LVs’ was lower in preterm-born versus term-born individuals at preterm-born children (WMD −0.73 cm/second; 95% CI −1.05 to −0.41; %WMD = −8.2%; P < .001). It did not differ significantly compared with that in term-born controls in young adulthood or in pooled analysis of children and adults. Preterm LVSVI was lower in young adulthood (Fig 4A) (WMD = −3.59 mL/m²; 95% CI −4.99 to −2.19; %WMD = −8.2%; P < .001). In stratification of preterm-born cases <32 weeks’ gestation, LVs’ was significantly lower compared with term-born controls in pooled data for children and young adults (WMD −0.61 cm/second; 95% CI −0.88 to −0.34; %WMD = −6.5%; P < .001), and LVF in young adulthood was significantly higher (WMD 1.08%; 95% CI 0.18 to 1.98; %WMD = 1.7%; P = .02), whereas LVSVI in young adulthood was even lower in those born at <32 weeks’ gestation (WMD −4.09 mL/m²; 95% CI −5.61 to −2.57; %WMD = −8.9%; P < .001).
TABLE 1 Summary of Meta-analyses for Primary Outcomes of Cardiac Structure and Function in Preterm-Born Individuals Compared With Term-Born Controls

<table>
<thead>
<tr>
<th>Outcome Parameter</th>
<th>Neonates, WMD (95% CI)</th>
<th>Infants, WMD (95% CI)</th>
<th>Children, WMD (95% CI)</th>
<th>Young Adults, WMD (95% CI)</th>
<th>Pooled Children and Young Adults, WMD (95% CI)</th>
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<tbody>
<tr>
<td><strong>LV e', cm/s</strong></td>
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<tr>
<td>PT versus T</td>
<td>−2.89 (−5.18 to −0.61)*</td>
<td>−1.58 (−3.80 to 0.44)</td>
<td>1.67 (−0.48 to 3.82)</td>
<td>0.66 (−0.16 to 1.48)</td>
<td>0.79 (0.02 to 1.55)*</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>−2.48 (−5.78 to 0.82)</td>
<td>−1.97 (−4.38 to 0.44)</td>
<td>1.67 (−0.48 to 3.82)</td>
<td>1.08 (0.18 to 1.98)*</td>
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<tr>
<td>≥32 wk versus T</td>
<td>−4.54 (−6.89 to −2.20)**</td>
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<td><strong>LV strain, %</strong></td>
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<tr>
<td>PT versus T</td>
<td>2.53 (0.08 to 4.99)*</td>
<td>1.55 (0.89 to 2.21)**</td>
<td>−0.57 (−1.52 to 0.37)</td>
<td>2.01 (−0.14 to 4.17)</td>
<td>0.70 (−1.13 to 2.54)</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>2.68 (0.10 to 5.25)**</td>
<td>1.80 (1.08 to 2.51)**</td>
<td>−0.57 (−1.52 to 0.37)</td>
<td>0.79 (−3.81 to 5.40)</td>
<td>0.06 (−2.27 to 2.40)</td>
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<tr>
<td><strong>LVEDVI, mL/m²</strong></td>
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<tr>
<td>PT versus T</td>
<td>2.41 (−6.59 to 1.78)</td>
<td>2.10 (0.98 to 3.21)**</td>
<td>0.57 (0.35 to 0.79)</td>
<td>0.13 (−0.19 to 0.45)</td>
<td>0.36 (0.10 to 0.61)*</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>1.75 (0.96 to 2.50)**</td>
<td>2.55 (1.82 to 3.27)**</td>
<td>0.57 (0.35 to 0.79)</td>
<td>0.20 (−0.07 to 0.47)</td>
<td>0.40 (0.19 to 0.61)**</td>
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<tr>
<td>≥32 wk versus T</td>
<td>0.17 (−0.73 to 1.08)</td>
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<tr>
<td><strong>LVMI, g/m²</strong></td>
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<tr>
<td>PT versus T</td>
<td>−1.82 (−2.71 to −0.92)**</td>
<td>3.51 (0.45 to 6.17)*</td>
<td>−4.84 (−7.47 to −2.21)**</td>
<td>4.80 (−1.80 to 11.40)</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>−2.71 (−4.74 to −0.68)**</td>
<td>4.68 (−1.25 to 10.81)</td>
<td>−4.84 (−7.47 to −2.21)**</td>
<td>3.64 (−3.63 to 10.91)</td>
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<tr>
<td>≥32 wk versus T</td>
<td>−1.96 (−2.71 to −0.62)**</td>
<td>3.07 (1.55 to 4.59)**</td>
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<tr>
<td><strong>RV e'</strong></td>
<td>−2.94 (0.54 to 5.35)</td>
<td>2.73 (0.89 to 4.57)**</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>3.87 (1.54 to 6.20)**</td>
<td>3.01 (0.81 to 5.22)**</td>
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<td><strong>RV strain, %</strong></td>
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<tr>
<td>PT versus T</td>
<td>−0.96 (−1.30 to −0.62)**</td>
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<tr>
<td>&lt;32 wk versus T</td>
<td>−1.52 (−2.23 to −0.80)**</td>
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<tr>
<td>≥32 wk versus T</td>
<td>−0.80 (−1.02 to −0.59)**</td>
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PT, preterm; T, term; wk, mean weeks’ gestation; —, not applicable.
* P < .05.
** P < .01.
*** P < .001.
a similar magnitude across all stages of development, with a pooled WMD in children and young adults of -1.05 cm/second (95% CI -1.46 to -0.65; %WMD = -5.9%; P < .001). Preterm E/e′ was higher in infants (WMD 2.10; 95% CI 0.98 to 3.21; %WMD = 23.9%; P < .001) and in childhood (WMD 0.57; 95% CI 0.35 to 0.79; %WMD = 11.2%; P < .001). Although E/e′ was higher in pooled data from preterm children and young adults, no significant difference was detected when just data from young adults born preterm were analyzed. There was no difference in E/A between groups in infancy and childhood, but it was significantly lower in preterm-born young adults compared with term-born controls (Fig 4B) (WMD -0.14; 95% CI -0.25 to -0.02; %WMD = -7.0%; P = .02).

In stratification of preterm-born cases <32 weeks’ gestation, LVEF deficits in comparison with term controls were numerically higher, with a WMD in pooled children and young adults of -1.12 cm/second (95% CI -1.54 to -0.70; %WMD = -6.3%; P < .001). Preterm E/e′ differences in young adulthood remained nonsignificant with stratification; however, differences between groups for pooled data of children and young adults were greater (WMD 0.40; 95% CI 0.19 to 0.61; %WMD = 7.7%; P < .001), and heterogeneity was lower (I² = 23%).

Evolution of LV Structure

LVMi was lower in preterm compared with term neonates (WMD -1.82 g/m²; 95% CI -2.71 to -0.92; %WMD = -8.9%; P < .001), although it was significantly higher in preterm infants compared with term infants (WMD 3.31 g/m²; 95% CI 0.45 to 6.17; %WMD = 11.7%; P = .02). LVPWd, although similar in neonates, was significantly higher in preterm compared with term infants (WMD 0.30 mm; 95% CI 0.16 to 0.43; %WMD = 9.4%; P < .001). Both LVMi (WMD -4.84 g/m²; 95% CI -7.47 to -2.21; %WMD = -9.0%; P < .001) and LVPWd (WMD -0.23 mm; 95% CI -0.44 to -0.01; %WMD = -4.0%; P = .04) were lower in preterm-versus term-born children. In young adulthood, there was a high I² in analyses (LVMi: I² = 93%; LVPWd: I² = 96%), with numerically higher LVMi in the preterm group that failed to reach statistical significance (WMD 4.80 g/m²; 95% CI -1.80 to 11.40; %WMD = 6.1%; P = .15).

LVEDD was smaller in preterm infants (WMD -2.25 mm; 95% CI -3.95 to -0.55; %WMD = -11.0%; P < .001), children (WMD -1.80 mm; 95% CI -2.97 to -0.64; %WMD = -4.7%; P = .002), and young adults (WMD -2.49 mm; 95% CI -4.26 to -0.72; %WMD = -4.9%; P = .006). In adulthood, both preterm LVEDVI (Fig 4C) (WMD -6.91 mL/m²; 95% CI -8.84 to -4.97; %WMD = -9.9%; P < .001) and LV length (WMD -0.56 cm; 95% CI -0.74 to -0.38; %WMD = -6.0%; P < .001) were significantly smaller than in term-born controls.

The magnitude of LVPWd differences in preterm versus term infants was greater in those born at <32 weeks’ gestation than those born at ≥32 weeks’ gestation (WMD 0.42 mm, 95% CI 0.14 to 0.70, %WMD = 14.0%; P = .004; versus WMD 0.20 mm, 95% CI 0.04 to 0.36, %WMD = 5.9%, P = .02). In analyses of young adults born preterm at <32 weeks’ gestation, LVPWd and LVMi remained
heterogeneous and nonsignificant compared with those in term-born controls, whereas the magnitudes of difference in LVEDD, LVEDVI, and LV length were larger.

**Meta-Regressions**

Meta-regression results are displayed in Supplemental Tables 5 and 6 and Supplemental Fig 1. In pooled analyses of neonates and infants, gestational age revealed a strong inverse relationship to LV systolic (LVs$'$; $P = .03$) and diastolic deficits (LVe$'$; $P < .001$; E/e$'$; $P < .001$). Within the limitations of there being a small number of studies in children and adults for these parameters, the results indicated that gestational age continued to be a strong determinant of lower LV systolic function (LVs$'$; $P < .001$); however, there was no significant relationship with LV diastolic function (LVe$'$; $P = .20$; E/e$'$; $P = .09$). The lower magnitude of RV strain was proportional to gestational age in pooled analyses of all developmental stages ($P = .002$). Meta-regression analyses for birth weight revealed similar significant relationships to LVs$'$, LVe$'$, E/e$'$, and RV strain. However, lower birth weight was the only variable associated with higher LVEF in preterm children and young adults ($P = .05$). Although the percentage of male participants did not significantly relate to LVMi, LVEF, LVe$'$, or E/e$'$ in meta-regression analyses, it was significantly related to LVs$'$ and LVEDD across developmental stages ($P < .05$).

Because the reporting of IUGR, SGA, and BPD incidence was incomplete, meta-regressions were not possible for all parameters, although BPD was significantly related to LVe$'$ in neonates and infants ($P = .001$). Lastly, 60% of the heterogeneity in LVMi changes in children and young adults born preterm was explained by postnatal age, indicating an increase in comparison with controls of 0.71 g/m$^2$ per year from childhood (95% CI 0.20 to 1.22; $P = .007$; $R^2 = 0.60$).

**DISCUSSION**

We present the first meta-analysis comparing cardiac structure and function between preterm-born cases and age-matched term-born controls from birth to young adulthood. Preterm-born individuals have persistently smaller ventricular dimensions, lower LV diastolic function that worsens with age, RV systolic impairment across all developmental stages, and an accelerated rate of LV hypertrophy from childhood to young adulthood. These cardiac alterations may make the myocardium more vulnerable to secondary insults, which may explain their increased risk of early heart failure and long-term risk of ischemic heart disease.

**Lower LV Systolic Function and Altered Morphology**

Preterm birth occurs during a key cardiac developmental period that normally occurs in utero and is associated with an increased risk of early heart failure in childhood to young adulthood, particularly in those born at earlier gestations.4 The results from this meta-analysis reveal that LVs$'$ is lower across gestational ages in neonates and remains lower in childhood and young adulthood in those born at $<32$ weeks' gestation. These subtle functional differences may make the preterm heart less resilient to common causes of early heart failure, such as myocarditis,57,58 potentially explaining part of the increased risk.

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**FIGURE 3**

Forest plots demonstrating differences in LVe$'$ in preterm-born individuals compared with term-born controls from neonatal life to young adulthood. WMDs are highlighted in bold and represented by diamonds. The size of data markers indicates the study weight with respective 95% CIs.
Biological variation associated with preterm birth, such as elevated blood pressure, abnormal vascular and respiratory development, and altered metabolic profile and immunity, will likely act as additional negative stimuli on their already compromised cardiac physiology. We believe that when exposed to adult cardiovascular risk, such as hypertension or myocardial injury, preterm-born adults will be more likely to develop heart failure. In further support of a reduced myocardial functional reserve, it has been shown by using echocardiography imaging at prescribed exercise intensities that preterm-born young adults have an impaired ability to increase LVEF and cardiac index under physiologic stress, which is suggestive of a reduced myocardial functional reserve. The greatest predictors of this reduced LV function during exercise were the degree of prematurity and smaller LVEDVI, primarily driven by shorter LV lengths. The results from our meta-analysis reveal consistently smaller LVEDVI and shorter LV length in young adulthood. Our finding that LVEF at rest is marginally higher in children and young adults born preterm should be interpreted cautiously. LVEF is not a direct measure of myocardial contractility, is strongly influenced by structural changes, and may be preserved or elevated despite systolic impairment in the setting of reduced LVEDVI.

Worsening Diastolic Phenotype and Accelerated Hypertrophy Rate

We report lower LV myocardial relaxation velocities throughout development, which may reflect greater myocardial fibrosis, as seen in animal models of preterm birth.

Although studies are needed to confirm this in humans, more fibrosis in the ventricular walls would alter myocardial viscoelastic properties, thereby decreasing compliance. Clinically, LV diastolic dysfunction is associated with a higher risk for invasive ventilation and pulmonary hemorrhage within the first day of life in premature infants, and it has a direct correlation to abnormal coupling of the RV to its afterload during the transitional period. As individuals progress to adulthood, reductions in diastolic function have diagnostic, therapeutic, and prognostic value. These measures are predictive of cardiovascular disease outcomes and disease progression, such as severity of heart failure. Continuous monitoring throughout life of diastolic function in preterm-born individuals therefore has immediate and long-term clinical value. Diastolic function may also be further worsened by myocardial hypertrophy. Compared with term controls, our meta-analysis reveals higher LVMi and wall thickness in preterm infants. LVMi is lower in preterm children, but there is an accelerated hypertrophy rate from childhood to young adulthood. Whether this worsens with natural aging and progression of the known greater blood pressure and cardiovascular risk factors in preterm-born individuals remains to be determined.

RV Systolic Impairment

Our meta-analyses reveal a greater right-sided systolic deficit with neonatal impairments in TAPSE approximately twofold greater than the corresponding LV measure MAPSE, revealing a persistent level of RV strain impairment throughout development that is proportional to gestational age. It is unlikely that early postnatal respiratory complications alone account for the
observed deficits in RV performance because the overall incidence of BPD was low, due to exclusion of studies stratified by BPD and exclusion of BPD cases when possible. Nevertheless, higher pulmonary vascular resistance in immature preterm lungs is expected to impose greater RV afterload in early life, whereas invasive measures of pulmonary elastance have confirmed increased RV afterload in preterm-born young adults.74 We, therefore, acknowledge that preterm RV systolic deficits may, in part, reflect the sensitivity of the thin-walled RV to loading conditions caused by preterm pulmonary abnormalities.

**Study Limitations**

The importance of these results should be interpreted within the framework of the inherent limitations of this meta-analysis. The causes of preterm birth and impact of preterm-related complications on cardiac structure and function could not be fully explored. It is possible that comorbidities, such as IUGR,53 may influence preterm cardiac phenotype. However, we demonstrated an inverse relationship between gestational age and impairments of LV and RV systolic function throughout development in analyses that excluded studies containing specific stratification for preterm-related complications. Although the majority of analyses were possible for our primary outcome measures, insufficient data statistically prevented the exploration of all intended measures at each developmental stage as well as stratification by gestational age >32 weeks and <32 weeks, highlighting the need for further research in the field. In addition, high $I^2$ values for some of the measures suggest that heterogeneity may have impacted some aspects of the meta-analysis. Furthermore, because analyses at each developmental stage are cross-sectional, we cannot make conclusions on whether alterations track throughout life in the same individuals, but rather we can only conclude that differences exist between groups at different developmental stages. Further longitudinal studies with serial cardiac imaging, including echocardiography and cardiovascular magnetic resonance, are needed to determine how cardiac remodeling in those born preterm progresses over time.

**CONCLUSIONS**

Individuals born preterm have a unique cardiac phenotype with persistent morphologic and functional differences across developmental stages from birth to young adulthood. These changes in cardiac structure and function may make the myocardium more vulnerable to secondary insults, contributing to an increased risk of early heart failure and ischemic heart disease. Given the high rates of preterm delivery and increasing survival rates,1,72 it is of particular public health interest to design primary prevention strategies for this growing cohort of susceptible individuals with newly recognized cardiovascular disease predisposition. Regular and long-term clinical cardiovascular follow-up of people born preterm is warranted and should be encouraged.

**ABBREVIATIONS**

BPD: bronchopulmonary dysplasia
CI: confidence interval
E/A: Doppler early/late diastolic mitral inflow velocity ratio
E/e’: early Doppler inflow velocity/peak early diastolic tissue velocity ratio
IUGR: intrauterine growth restriction
LV: left ventricular
LVe’: left ventricular peak early diastolic tissue velocity
LVEDD: left ventricular end-diastolic dimension
LVEDVI: left ventricular end-diastolic volume indexed to body surface area
LVFS: left ventricular fractional shortening
LVMI: left ventricular mass indexed to body surface area
LVPWd: left ventricular posterior wall thickness at end diastole
LVs’: left ventricular peak systolic tissue velocity
LVSVI: left ventricular stroke volume indexed to body surface area
MAPSE: mitral annular plane systolic excursion
RV: right ventricular
RVe’: right ventricular peak early diastolic tissue velocity
RVs’: right ventricular peak systolic tissue velocity
SGA: small for gestational age
TAPSE: tricuspid annular plane systolic excursion
WMD: weighted mean difference
%WMD: percentage weighted mean difference
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