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An overview of adult health outcomes after preterm birth

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ABSTRACT

Preterm birth (gestational age < 37 completed weeks) has increased in prevalence in most countries in the past 20 years and now affects nearly 11% of all births worldwide. Because of treatment advances introduced in the 1970s–1980s, > 95% of preterm infants who receive modern neonatal and pediatric care now survive into adulthood. The earliest birth cohorts to benefit from those advances are now in their 4th and 5th decades of life. A growing number of large cohort studies have investigated the long-term health sequelae in adulthood. Evidence has consistently shown that adult survivors of preterm birth have increased risks of chronic disorders involving various organ systems, including cardiovascular, endocrine/metabolic, respiratory, renal, neurodevelopmental, and psychiatric disorders, which either persist from childhood into adulthood or sometimes first manifest in adulthood. These disorders also lead to moderately (30% to 50%) increased mortality risks during early to mid-adulthood among persons born preterm compared with full-term, and even higher risks among those born at the earliest gestational ages. However, the majority of persons born preterm have low absolute risks of these outcomes and good self-reported quality of life in adulthood. Priorities for future research include the assessment of long-term health sequelae of preterm birth in racially and economically diverse populations, additional follow-up of existing cohorts into older adulthood, elucidation of outcomes by preterm birth subtype (e.g., different underlying causes) to improve risk stratification, and identification of protective factors that will support the long-term health trajectory and well-being of preterm-born adults.

1. Introduction

Preterm birth (gestational age < 37 completed weeks) has increased in prevalence over the past few decades in almost all countries with reliable trend data [1]. In 2014, preterm birth had a worldwide prevalence of 10.6%, affecting nearly 15 million births annually [2]. Because of treatment advances introduced in the 1970s–1980s [3,4], survival of preterm infants also has improved dramatically. Over 95% of preterm infants and the majority of those born extremely preterm (< 28 weeks) who receive modern neonatal and pediatric care now survive into adulthood (ages ≥ 18 years) [5–8]. As a result, millions of preterm birth survivors are now transitioning to adulthood each year worldwide. A comprehensive understanding of their long-term health sequelae is needed to inform counseling of these patients and their families and to guide their follow-up care across the life course.

In the past 10 years, the number of peer-reviewed articles published annually on adult health outcomes after preterm birth has approximately doubled. In 2015, the U.S. National Institutes of Health hosted a working group conference on “Adults Born Preterm: Epidemiology and Biological Basis for Adult Outcomes” [5]. Several hundred additional

relevant studies have been published since then. The present article will review the current evidence. Much of the evidence to date comes from registry-based studies particularly in Nordic countries, which have the advantages of large national cohorts with nearly complete birth data, several decades of follow-up into adulthood, and little loss to follow-up. This article will provide an overview of (1) all-cause and cause-specific mortality in adults who were born preterm, (2) specific major chronic disease outcomes (cardiovascular, endocrine/metabolic, respiratory, renal, neurodevelopmental, and psychiatric disorders) in adulthood, (3) the prevalence of good health outcomes in adulthood after preterm birth, and (4) key priorities for future research.

2. All-cause mortality

Large cohort studies have shown that among persons born in the modern neonatal care era who survived to adulthood (≥ 18 years), those born preterm had approximately 30% to 50% higher all-cause mortality in early to mid-adulthood (ages ranging from 18 to 45 years) than those born full-term [9]. A recent systematic review [9] identified 7 published studies (5 in Sweden [6,7,10–12], 1 in Norway [13], and 1

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in Australia [14]) that examined preterm birth in relation to all-cause mortality in adulthood. After adjusting for other perinatal and socio-demographic factors, most relative risks were in the 1.2 to 1.6 range [9].

The largest study to date included > 4 million persons born as singletons in Sweden during 1973–2015 who were followed up through 2017 (including > 2.5 million who reached adult ages) [6]. All-cause mortality in adulthood was assessed separately at ages 20–29 and 30–45 years. Adjusted hazard ratios (HRs) for all-cause mortality associated with preterm birth among women and men, respectively, were 1.54 (95% CI, 1.31–1.82; $P < 0.001$) and 1.32 (1.20–1.46; $P < 0.001$) at ages 20–29 years, and 1.55 (1.28–1.89; $P < 0.001$) and 1.17 (1.01–1.34; $P = 0.03$) at ages 30–45 years, compared with full-term birth (39–41 weeks). Extremely preterm birth (22–27 weeks) was associated with 2-fold mortality at ages 20–29 or 30–45 years. Most HRs were higher among women because of lower background mortality in those born at term compared with men. However, preterm birth accounted for significantly more total deaths among men (additive interaction, $P < 0.001$). In addition, a co-sibling analysis to control for unmeasured shared familial factors in 3.5 million persons with at least one sibling showed minimal change in risk estimates, suggesting that the observed associations were not due to confounding by shared genetic or environmental factors in families [6]. Fig. 1 shows the adjusted HRs for all-cause mortality from birth to age 45 years associated with gestational age at birth in this large cohort [6].

Attributable risks also were recently estimated using data from the same large cohort in Sweden [9]. Preterm and extremely preterm birth, respectively, accounted for an estimated 20.8 (95% CI, 16.4–25.1) and 52.8 (11.2–94.4) additional deaths per 100,000 person-years at ages 18–45 years, compared with full-term birth. An estimated 29.7% and 51.8% of deaths at ages 18–45 years among those born preterm or extremely preterm, and 2.6% and 0.1% of deaths in the entire population, were attributable to preterm or extremely preterm birth, respectively. Among all studies to date, the overall findings indicate that preterm birth is independently associated with modestly increased all-cause mortality in early to mid-adulthood [9].

3. Cause-specific mortality

Associations between preterm birth and cause-specific mortality have been explored only in Swedish [6,7,10,12] and Norwegian [13] cohorts. The largest cohort included > 4 million persons born as singletons in Sweden during 1973–2015, followed up through 2017 [6]. Low gestational age at birth was associated with higher risks of all major causes of death (including respiratory, cardiovascular, endocrine, neurological, cancer, and external causes) from birth to age 45 years among both males and females [6]. Whereas respiratory disorders,

congenital anomalies, and other perinatal causes predominated in childhood, associations with endocrine, cardiovascular, and neurological mortality were observed in young adulthood (ages 20–29 years), and strong associations with endocrine (mostly diabetes) and respiratory mortality extended further into adulthood (adjusted HRs at ages 30–45 years per additional 1 week of gestation, endocrine: 0.85; 95% CI, 0.79–0.92; $P < 0.001$; respiratory: 0.87; 0.80–0.95; $P < 0.001$).

Associations with cause-specific mortality also were explored in a Norwegian cohort of 1.5 million persons born in 1967–1997, who were followed up to a maximum age of 45 years [13]. Very preterm birth (< 34 weeks) was associated with modestly increased mortality from external causes (adjusted HR, 1.20; 95% CI, 1.01–1.43), which appeared to involve both accidents/violence and suicide, and with non-significantly increased mortality from cardiovascular disease (1.58; 0.94–2.64) and cancer (1.30; 0.97–1.93). In an earlier birth cohort of 11,474 persons born as singletons in 1915–1929 in Uppsala, Sweden, who were followed up to a maximum age of 86 years, low gestational age at birth was associated with higher risk of death from cerebrovascular disease (P for linear trend = 0.03) and specifically occlusive stroke ($P = 0.02$), but not ischemic heart disease ($P = 0.16$), although statistical power was limited [15]. The overall evidence to date suggests that preterm birth is associated with increased mortality in early to mid-adulthood because of several major causes, including cardiovascular, respiratory, endocrine, and neurological disorders [9].

4. Cardiovascular disorders

4.1. Hypertension

Epidemiologic studies have consistently linked preterm birth with higher blood pressure in adulthood. A meta-analysis of 27 studies with 17,030 preterm- and 295,261 term-born young adults (mean age 19.6 years) reported that preterm birth was associated with higher systolic blood pressure (SBP) by 4.2 mmHg (95% CI, 2.8–5.7) and higher diastolic blood pressure (DBP) by 2.6 mmHg (1.2–4.0), with stronger effects among women [16]. Another pooled analysis of 9 cohorts with 1571 young adults born at very low birth weight (< 1500 g) and 777 controls reported similar findings: preterm birth was associated with higher SBP by 3.4 mmHg (95% CI, 2.2–4.6) and higher DBP by 2.1 mmHg (1.3–3.0), with slightly stronger effects among women [17]. A UK study of 7847 adults aged 44–45 years reported that each additional week of gestation was associated with a lower SBP by 0.53 mmHg on average (95% CI, 0.32–0.75) [18]. In a Swedish cohort of 636,552 adults aged 25–37 years, preterm birth was associated with significantly increased prescription of antihypertensive medications [19].

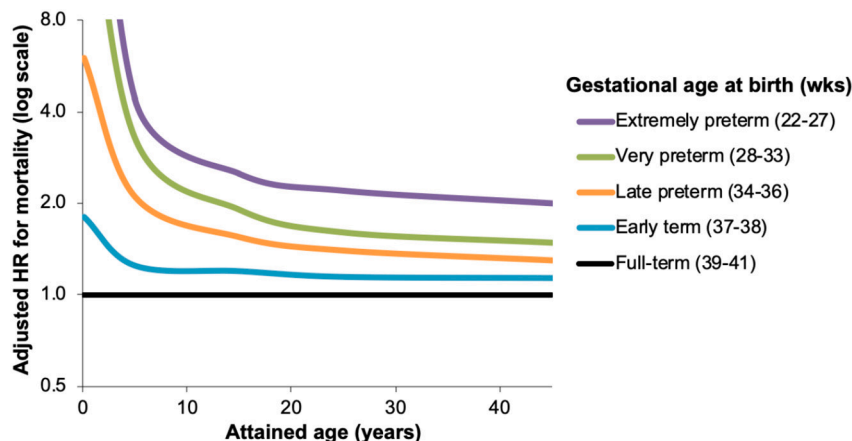


Fig. 1. Adjusted hazard ratios for all-cause mortality from birth to age 45 years by gestational age at birth compared with full-term, 1973–2017, Sweden.

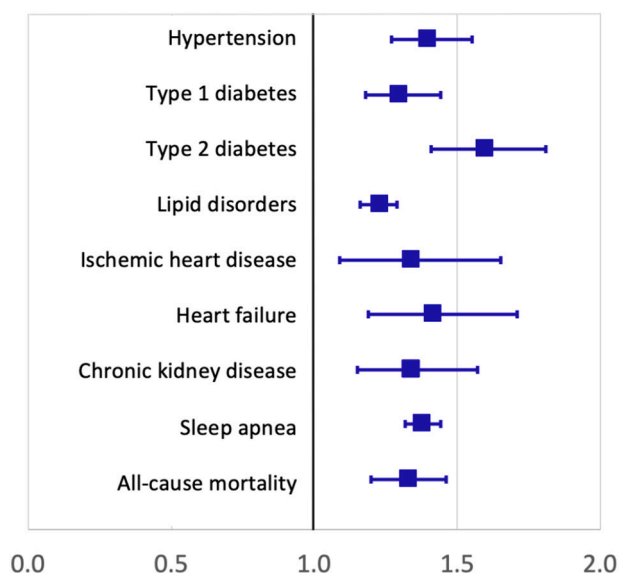


Fig. 2. Adjusted hazard ratios and 95% CIs for associations between preterm birth and health outcomes at ages 18–45 years compared with full-term, 1973–2015, Sweden.

The largest study of hypertension to date included > 4 million persons born as singletons in Sweden during 1973–2014, who were followed up for hypertension identified from nationwide inpatient and outpatient (both specialty and primary care) diagnoses through 2015 (maximum age 43 years) [20]. Adjusted HRs for new-onset hypertension at ages 18–29 years associated with preterm and extremely preterm (22–27 weeks) birth were 1.28 (95% CI, 1.21–1.36) and 2.45 (1.82–3.31), respectively, and at ages 30–43 years were 1.25 (1.18–1.31) and 1.68 (1.12–2.53), respectively, compared with full-term birth (39–41 weeks). These associations affected men and women similarly. Co-sibling analyses suggested that they were largely (60% to 80%) related to shared genetic and/or environmental factors in families [20]. Both spontaneous and medically indicated preterm birth were associated with increased risks of hypertension compared with full-term birth (adjusted HR, 1.17; 95% CI, 1.08–1.27; $P < 0.001$; and 1.35; 1.23–1.48; $P < 0.001$, respectively) [20]. Fig. 2 shows adjusted HRs and 95% CIs for hypertension and other chronic disorders in adulthood associated with preterm birth in the same large Swedish cohort.

4.2. Ischemic heart disease

Despite evidence linking preterm birth with hypertension [16–20] and other cardiovascular risk factors [16,21–23], most early studies of preterm birth and risk of ischemic heart disease (IHD) were either null or inconclusive. For example, a Finnish study of 19,015 persons born in 1924–44 reported no association between preterm birth and IHD risk (adjusted HR, 1.03; 95% CI, 0.89–1.18) [24]. A Swedish study of 1.3 million persons born in 1983–1995 with follow-up to ages 15–27 years reported a non-significant association with IHD risk (adjusted HR comparing 32–36 vs. 37–41 weeks: 1.44; 95% CI, 0.81–2.56) [25]. Another Swedish study of 1.9 million persons (maximum age 38 years) reported a borderline-significant association between preterm birth and IHD risk adjusted for age and sex (HR, 1.36; 95% CI, 1.00–1.85), and no association when further adjusted for other perinatal, familial, and comorbidity factors [26].

However, previous findings were potentially affected by insufficient follow-up into adulthood or possible survivor bias in the earliest birth cohorts (i.e., the strongest infants who survived may be less susceptible to IHD later in life than more recent survivors). A more recent national cohort study included > 2 million persons born as singletons in Sweden during 1973–1994, who were followed up for IHD identified from

nationwide inpatient and outpatient diagnoses through 2015 (maximum age 43 years) [27]. Preterm birth was associated with increased risks of IHD in adulthood that were higher after longer follow-up times. The adjusted HRs for IHD associated with preterm birth were 1.32 (95% CI, 0.99–1.76) at ages 18–29 years and 1.53 (1.20–1.94) at ages 30–43 years, compared with full-term birth (39–41 weeks). These risks were even higher among women, likely due to a lower background incidence of IHD in those born at term compared with men. Co-sibling analyses suggested that these associations were not explained by confounding from unmeasured shared genetic or early-life environmental factors in families [27]. This evidence from the largest cohort to date indicates that preterm birth survivors have increased risks of IHD that begin to emerge in early adulthood. These findings also suggest the possibility that known racial/ethnic disparities in preterm birth might contribute significantly to cardiovascular health disparities across the life course [28].

4.3. Other cardiovascular outcomes

Other cardiovascular outcomes in adulthood have been less frequently studied. Preterm birth was associated with increased risk of heart failure at ages 1–27 years in a Swedish cohort of 2.6 million persons born in 1987–2012 (adjusted HR, < 28 weeks: 17.0; 95% CI, 8.0–36.3; 28–31 weeks: 3.6; 1.6–8.1; 32–36 weeks: 1.4; 0.9–2.1, compared with ≥ 37 weeks) [29]. Preterm birth also was associated with increased risk of venous thromboembolism at ages 18–38 years in a Swedish cohort of 3.5 million persons born in 1973–2008 (adjusted HR, < 28 weeks: 2.8; 95% CI, 1.4–5.3; 28–33 weeks: 1.5; 1.2–1.9; 34–36 weeks: 1.2; 1.1–1.4, compared with 37–41 weeks) [30]. An association between preterm birth and increased risk of stroke in adulthood was reported in some [25] but not all [24,31] studies, and was limited to those born at the earliest gestational ages.

5. Endocrine/metabolic disorders

5.1. Diabetes mellitus

Preterm birth has consistently been linked with increased risks of both type 1 and type 2 diabetes later in life [21,22,32–35]. A large meta-analysis reported pooled odds ratios of 1.18 (95% CI, 1.11–1.25) for type 1 diabetes (based on 18 studies with 2,176,480 participants, mostly aged < 15 years) and 1.51 (1.32–1.72) for type 2 diabetes (based on 5 studies with 31,478 participants, mostly middle-aged adults) [21]. A more recent study with the largest cohort to date yielded very similar risk estimates specifically in adulthood. This study included > 4 million persons born as singletons in Sweden during 1973–2014 who were followed up for type 1 and type 2 diabetes identified from nationwide outpatient, inpatient, and pharmacy data through 2015 (including > 2.5 million persons who reached adult ages) [22]. Preterm birth was associated with approximately 1.2- and 1.5-fold risks of new-onset type 1 and type 2 diabetes, respectively, at ages 18–43 years (adjusted HR, type 1: 1.24; 95% CI, 1.13–1.37; type 2: 1.49; 1.31–1.68). Extremely preterm birth was associated with > 2-fold risks of both type 1 and type 2 diabetes in adulthood. The associations between preterm birth and type 2 (but not type 1) diabetes were significantly stronger in women ($P < 0.01$). Co-sibling analyses suggested that the findings for type 2 diabetes were independent of shared familial (genetic and/or environmental) factors, whereas those with type 1 diabetes were partially (~40%) explained by such factors [22]. In addition, both spontaneous and medically indicated preterm birth were associated with increased risks of type 1 diabetes (adjusted HR, 1.22; 95% CI, 1.11–1.34; and 1.22; 1.09–1.37, respectively) and type 2 diabetes (1.41; 1.05–1.90; and 1.45; 1.02–2.04, respectively) [22].

These findings are consistent with those from other smaller studies. A Swedish cohort study of 630,090 adults aged 25–37 years found that those born preterm had modestly (10–25%) increased odds of

medication prescription for diabetes that was predominantly type 1 [36]. Several other studies have reported associations between preterm birth and type 2 diabetes in mid-adulthood. For example, a Finnish cohort study of 12,813 adults aged > 40 years reported a 1.6-fold (95% CI, 1.00–2.52) risk among those born at < 35 vs. 37–41 weeks [37]. A Swedish cohort study of 6425 adults aged 37–62 years reported that those born at < 33 weeks had a 1.6-fold (95% CI, 1.33–2.11) risk of type 2 diabetes based on inpatient diagnoses [38]. A Scottish cohort study of 5973 adults aged 46–50 years reported that preterm birth was associated with a 2-fold (95% CI, 1.18–3.53) risk of self-reported type 2 diabetes [39].

5.2. Lipid disorders

Preterm birth also has been linked with increased risks of lipid disorders and cardiometabolic syndrome in adulthood [16,23]. The largest study of lipid disorders included 2.2 million persons born as singletons in Sweden during 1973–1995 who were followed up for lipid disorders identified from outpatient, inpatient, and pharmacy data through 2016 [23]. Preterm and extremely preterm (22–27 weeks) birth were associated with 1.2- and 2-fold risks of lipid disorders, respectively, at ages 18–44 years (adjusted HRs, 1.23; 95% CI, 1.16–1.29; $P < 0.001$; and 2.00; 1.41–2.85; $P < 0.001$). These associations were similar among men and women. Co-sibling analyses suggested that they were partially (~55%) related to unmeasured shared familial factors that are associated with both preterm birth and lipid disorders, as opposed to direct effects of preterm birth [23].

A meta-analysis of previous smaller studies found that preterm birth was associated with significantly higher LDL levels compared with full-term birth (0.15 mmol/L; 95% CI, 0.01 to 0.30; $P = 0.04$; based on 5 studies), and near-significantly higher total cholesterol levels (0.32 mmol/L; -0.01 to 0.65; $P = 0.05$; 6 studies), but no differences in HDL or triglyceride levels (8 and 9 studies, respectively) [16].

6. Respiratory disorders

6.1. Reduced pulmonary function

Preterm birth is associated with reduced pulmonary function that may persist into early adulthood and is more pronounced in those with a history of bronchopulmonary dysplasia (BPD). A meta-analysis of 59 studies involving children and/or young adults reported that expiratory airflow (%FEV₁, percentage predicted forced expiratory volume in 1 s) was significantly reduced in those born preterm either with or without BPD [40]. Compared with term controls, the mean %FEV₁ was 7.2% (95% CI, 5.6% to 8.7%) lower in persons born preterm without BPD, 16.2% (12.4% to 19.9%) lower in those with BPD who required supplemental oxygen for > 28 days, and 18.9% (16.7% to 21.1%) lower in those with BPD who required supplemental oxygen for > 36 weeks [40].

In a systematic review of 14 studies that included young adults, all studies found that survivors of BPD who were born either preterm or with very low birthweight had reduced pulmonary function, increased respiratory symptoms, and/or radiologic abnormalities that persisted into adulthood [41]. A Finnish study with 719 participants reported that early preterm (< 34 weeks) but not late preterm (34–36 weeks) birth in the presurfactant era was associated with substantially reduced expiratory airflow in young adulthood (mean age 23 years), even after excluding those with BPD [42]. An Australian study with 294 participants found that extremely preterm birth in the postsurfactant era also was linked with substantially reduced expiratory airflow at age 25 years, which was more severe in those with BPD [43]. A meta-analysis of 11 studies reported that persons born very preterm or with very low birthweight (mostly in the presurfactant era) had substantially reduced expiratory airflow at a mean age of 23 years [44].

6.2. Long-term obstructive lung disease

Preterm birth survivors, either with or without BPD, have increased frequency of respiratory symptoms commonly reported as asthma and increased bronchodilator use early in life [45]. These outcomes may persist into adulthood, although previous findings are inconsistent [42,46–48]. A Swedish national cohort study of 622,616 persons born in 1973–1979 found that extremely preterm birth was associated with more than a 2-fold risk of asthma medication prescription at ages 25–35 years compared with term birth [49]. Other smaller studies of young adults in Norway (ages 20–24 years) [50] and the UK (ages 18–25 years) [51] reported non-significant associations between preterm birth and asthma symptoms or diagnosis. A survey of 5192 Finnish adults aged 31 years reported no association between preterm birth and asthma [52]. A retrospective cohort study of 149,398 Swedish males aged 17–20 years also did not confirm an association between preterm birth and physician-diagnosed asthma [53]. Preterm birth and BPD combined with harmful environmental exposures may potentially lead to higher risks of chronic obstructive pulmonary disease (COPD) later in adulthood [54], but large cohort studies with longer follow-up times are needed for more definitive assessment.

6.3. Respiratory infections

Because of pulmonary and immune system immaturity, preterm children are more susceptible to respiratory viral infections and their complications [55,56], which may contribute to persistently reduced lung function later in life [57]. However, risks of respiratory infections and their complications have rarely been explored in adult survivors of preterm birth. A Swedish cohort analysis of 674,820 persons born in 1973–1979 found that preterm birth was associated with increased mortality attributed to infections (which were predominantly respiratory) at ages 29–36 years [58]. New population-based studies will be needed to assess the risks of complications and mortality associated with the novel virus SARS-CoV-2 in preterm-born children and adults.

6.4. Sleep-disordered breathing

A Swedish cohort study of > 4 million persons examined whether preterm birth is associated with increased risk of sleep-disordered breathing (SDB), as identified from nationwide outpatient and inpatient diagnoses [59]. After adjusting for other perinatal and maternal factors, preterm birth was associated with approximately 1.4-fold risks of SDB at either ages 20–29 years (adjusted HR, 1.36; 95% CI, 1.30–1.42; $P < 0.001$) or 30–43 years (1.40; 1.34–1.47; $P < 0.001$), compared with full-term birth (39–41 weeks). Extremely preterm birth (22–27 weeks) was associated with 2-fold risks of SDB in adulthood. These associations were found in both males and females, although preterm birth accounted for more SDB cases in males (additive interaction, $P = 0.003$). Co-sibling analyses suggested that these findings were largely independent of unmeasured shared genetic or environmental factors in families. This evidence from a large national cohort suggests that preterm birth is an independent risk factor for SDB in early to mid-adulthood [59].

SDB symptomatology has rarely been explored in adult survivors of preterm birth. However, a Finnish case-control study reported a > 2-fold odds of chronic snoring among 158 young adults (ages 18–27 years) born preterm with very low birthweight (< 1500 g) compared with 167 term controls (adjusted odds ratio, 2.21; 95% CI, 1.07–4.54) [60].

7. Kidney disease

Preterm birth interrupts fetal nephrogenesis, resulting in a lower nephron endowment [61,62] and heightened susceptibility to chronic kidney disease (CKD) later in life. A recent national cohort study

examined the risk of CKD identified from outpatient and inpatient diagnoses in > 4 million persons born as singletons in Sweden during 1973–2014 who were followed up through 2015 [63]. After adjusting for other perinatal and maternal factors, persons born preterm or extremely preterm had nearly 2-fold and 3-fold risks of CKD, respectively, from birth to age 43 years. These associations were strongest in childhood, then weakened but remained substantially elevated in adolescence and adulthood. Males and females were similarly affected. Among persons who survived to age 20 years, those born preterm had a 1.3-fold risk of CKD at ages 20–43 years compared with those born full-term (adjusted HR, 1.34; 95% CI, 1.15–1.57; $P < 0.001$). Co-sibling analyses suggested that these findings were not due to shared genetic or environmental factors in families, but rather to direct effects of preterm birth [63].

Other studies have linked low birthweight (< 2500 g) with higher risk of CKD in adulthood, without specifically examining gestational age at birth. A meta-analysis of 18 such studies reported a pooled odds ratio of 1.7 (95% CI, 1.4–2.1) [64]. The largest of those was a Norwegian cohort study of 2.2 million births, which reported that small for gestational age was associated with an increased risk of end-stage renal disease (ESRD) at ages up to 38 years (HR, 1.5; 95% CI, 1.2–1.9) [65]. In an overlapping Norwegian cohort of 1.8 million births, low birthweight was associated with an increased risk of ESRD at ages up to 42 years (adjusted HRs 1.6 to 1.8), which appeared to be unrelated to shared familial factors, and preterm birth was associated with a non-significantly increased risk of ESRD (adjusted HR, 1.3; 95% CI, 0.8–2.0) [66].

8. Neurodevelopmental disorders

Preterm birth is the most commonly reported cause of cerebral palsy and has been associated with other lifelong neurodevelopmental disorders. A meta-analysis of 26 studies reported a nearly 15% prevalence of cerebral palsy in those born extremely preterm (< 28 weeks) [67]. Preterm birth survivors also have increased risks of cognitive impairment [68,69]. Those born very preterm (< 32 weeks) or with very low birthweight (< 1500 g) have been reported to have lower head circumference at birth (mean difference, 7.5 cm) and lower IQ at age 26 years (mean difference, 13.6) compared with term controls [70]. Severe visual or hearing loss has been reported in 2% to 5% of those born extremely preterm [71,72]. Cohort studies in Sweden [11] and the US [73] have reported approximately 3-fold risks of autism among persons born extremely preterm compared with full-term.

Preterm birth also has been associated with epilepsy among young adults, either with or without neurodevelopmental comorbidities. In a Swedish cohort of 630,090 persons born in 1973–1979, the relative odds of hospitalization for epilepsy at ages 25–37 years was markedly increased even for those born at 35–36 weeks and increased monotonically by earlier gestational ages, including a 5-fold risk among those born at 23–31 weeks [74]. These associations were independent of fetal growth and other perinatal or familial factors, and were present even in those without cerebral palsy or other known neurological disorders [74].

9. Psychiatric disorders

Preterm birth interrupts normal brain development during a period of rapid growth and may increase lifelong susceptibility to psychiatric disorders. Adult survivors of preterm birth have been reported to have increased risks of depression, anxiety, bipolar disorder, and non-affective psychosis [75–77]. A Swedish study of 1.3 million persons born in 1973–1985 reported that those born preterm had significantly higher risks of hospitalization for psychiatric disorders (including depression, bipolar disorder, and nonaffective psychosis) at ages 17–30 years, with most relative risks in the 1.5 to 3 range [77]. These findings were consistent with those from another Swedish study of

545,628 persons born in 1973–1979, which reported a stepwise increase in risk of psychiatric hospitalization at ages 8–29 years by earlier gestational age at birth [78]. Other studies have reported increased risks of attention deficit hyperactivity disorder (ADHD) [79] and eating disorders [80] in young adults who were born preterm. In contrast, preterm birth has been associated with reduced risks of anti-social behavior [81], risk-taking behaviors [82], and substance use disorders [11].

A Swedish national cohort study of 635,933 persons born in 1973–1979 examined whether preterm birth was associated with psychotropic medication prescription in young adulthood (ages 25–34 years) [83]. After adjusting for sociodemographic confounders, those born extremely preterm (23–27 weeks) had a 3.1-fold odds of antipsychotic prescription (95% CI, 1.66–5.93), 1.8-fold odds of antidepressant prescription (1.26–2.64), and 1.8-fold odds of hypnotic/sedative prescription (1.15–2.96) compared with those born at term. A Norwegian study of 450,555 persons born in 1974–1984 also found that preterm birth was associated with increased risks of anxiolytic, hypnotic, antipsychotic, as well as antiepileptic prescription at age 30 years [84]. A systematic review of 13 studies of persons born in 1977–1995 with follow-up to ages 18–35 years found consistent evidence that those born very preterm or with very low birthweight had increased risks of any psychotropic medication use, and mixed evidence for higher risks of mental disorders that first appeared in adulthood [85].

10. Prevalence of good health outcomes

Several studies have suggested that despite having more functional limitations, young adults who were born preterm or with low birthweight frequently report a high subjective quality of life that is similar to their full-term or normal birthweight counterparts [86–89]. A systematic review of 18 studies from 11 countries examined self-reported health-related quality of life among adults aged 18–36 years who were born very preterm (< 32 weeks) or with very low birthweight (< 1500 g) compared with term controls [90]. Eleven studies that were determined to have sufficient rigor reported no differences, whereas 4 studies reported lower quality of life in those born very preterm or with very low birthweight, and 3 were inconclusive [90].

A recent national cohort study examined the prevalence of survival without any major comorbidities in 2.5 million persons born during 1973–1998 in Sweden who were followed up to ages 18–43 years [8]. Major comorbidities were assessed using the Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) Comorbidity Index, comprised of 43 chronic disorders that commonly manifest in adolescence or young adulthood [8,91]. The majority (54.6%) of persons born preterm and 22.3% of those born extremely preterm (22–27 weeks) were still alive without any major comorbidities at ages 18–43 years, compared with 63.0% of those born full-term ($P < 0.001$ for each comparison) [8]. These findings were similar among men and women, and appeared independent of birth year and other perinatal or maternal factors. When comorbidities were alternatively assessed using the Charlson Comorbidity Index [92], 73.1% of those born preterm and 32.5% of those born extremely preterm survived into adulthood without any major comorbidities, compared with 81.8% of those born full-term, which also were significant differences ($P < 0.001$ for each). Co-sibling analyses suggested that these differences were not explained by unmeasured shared genetic or environmental factors in families. The relatively high prevalence (> 50%) of survival without major comorbidities among preterm-born adults reflects both the treatment advances that have occurred in the past 50 years and the resilience of preterm survivors in maintaining good health. However, those born at the earliest gestational ages face significantly greater long-term health and social challenges [8]. Fig. 3 shows the prevalence of survival into adulthood without any major comorbidities (based on the AYA HOPE Index) by gestational age at birth and birth decade in this large cohort [8].

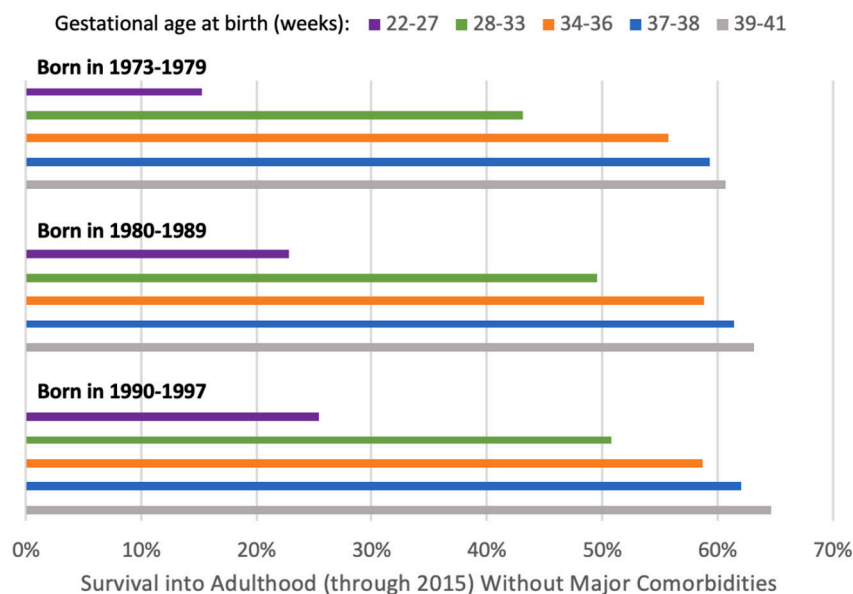


Fig. 3. Prevalence of survival without any major comorbidities (ages 18–43 years) by gestational age at birth and birth decade, 1973–2015, Sweden.

11. Future directions

The present overview reveals several priorities for future research. First, most evidence on adult outcomes after preterm birth has originated from cohorts in a few high-income populations, especially in Nordic countries [93]. However, those populations have a lower prevalence of preterm birth [2] as well as other sociodemographic and health care differences compared with the US and many other countries. New studies will be needed in other populations when feasible, including in low- and middle-income countries, to explore the long-term sequelae of preterm birth and potential heterogeneity in racial/ethnic subgroups. Second, additional follow-up of existing cohorts will be needed to assess outcomes in later adulthood as such data become available. Increased risks of IHD associated with preterm birth were only recently identified after follow-up times were extended into mid-adulthood [27], and other important associations may potentially emerge with follow-up to older ages. Third, most large cohort studies have lacked highly detailed or complete information on underlying causes of preterm birth. Studies with additional data on preterm birth subtypes that include follow-up into adulthood are a high priority to further elucidate mechanisms and improve long-term risk stratification. Lastly, studies with access to data on lifestyle factors later in life (e.g., physical activity, diet, obesity, alcohol or other substance use, social networks) are needed to assess their potential modifying effects on long-term outcomes in preterm-born adults. Such studies may help further identify protective factors that enhance resilience and well-being across the life course.

12. Conclusions

A rapidly growing body of research indicates that preterm birth is associated with higher risks of cardiovascular, endocrine/metabolic, respiratory, renal, neurodevelopmental, and psychiatric disorders in early to mid-adulthood. These associations also lead to moderately increased mortality risks among men and women who were born preterm [6,7,9]. However, despite these increased risks, the majority of persons born preterm survive into adulthood without major comorbidities [8] and report a good health-related quality of life [90].

Preterm birth should be recognized as a chronic condition that requires long-term follow-up to facilitate preventive actions and timely detection and treatment of adverse sequelae across the life course [4,6]. Gestational age and other birth history should be routinely included in

history-taking and medical records for patients of all ages [94–96]. Such information can provide additional valuable context for understanding patients' health and help trigger counseling and anticipatory screening in those born preterm [94]. High priorities for future research include the assessment of long-term sequelae of preterm birth in racially and economically diverse populations, further risk stratification by preterm birth subtype, and identification of protective factors that will support the long-term health trajectory of preterm birth survivors.

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Declaration of competing interest

We declare that we have no conflicts of interest.

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