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Preterm Birth and Risk of Heart Failure Up to Early Adulthood

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ABSTRACT

BACKGROUND In small clinical studies, preterm birth was associated with altered cardiac structure and increased cardiovascular mortality in the young.

OBJECTIVES The goal of this study was to determine the association between preterm birth and risk of incident heart failure (HF) in children and young adults.

METHODS This register-based cohort study included 2,665,542 individuals born in Sweden from 1987 to 2012 who were followed up from 1 year of age to December 31, 2013. The main study outcome was diagnosis of HF in the National Patient Register or the Cause of Death Register. The association between preterm birth and risk of incident HF was analyzed by using a Poisson regression model. Estimates were adjusted for maternal and pregnancy characteristics, socioeconomic status, and maternal and paternal cardiovascular disease.

RESULTS During 34.8 million person-years of follow-up (median 13.1 years), there were 501 cases of HF. After exclusion of 52,512 individuals with malformations (n = 196 cases), 305 cases of HF remained (0.88 per 100,000 person-years). Gestational age was inversely associated with the risk of HF. Compared with individuals born at term (≥37 weeks' gestation), adjusted incidence relative risks for HF were 17.0 (95% confidence interval [CI]: 7.96 to 36.3) after extremely preterm birth (<28 weeks) and 3.58 (95% CI: 1.57 to 8.14) after very preterm birth (28 to 31 weeks). There was no risk increase after moderately preterm birth (32 to 36 weeks) (relative risk: 1.36; 95% CI: 0.87 to 2.13).

CONCLUSIONS There was a strong association between preterm birth before 32 weeks of gestation and HF in childhood and young adulthood. Although the absolute risk of HF is low in young age, our findings indicate that preterm birth may be a previously unknown risk factor for HF. (J Am Coll Cardiol 2017;69:2634–42) © 2017 by the American College of Cardiology Foundation.

Between 5% and 13% of all live births occur before term (<37 weeks of gestation) (1,2). Although prematurity is still the main cause of neonatal death globally, high-income countries have experienced dramatic increases in survival rates in preterm infants over the past few decades (2,3). Knowledge about how the burdens of prematurity may be carried into later life in these steadily growing generations of new survivors is important for improving neonatal care, for meeting the future medical needs of these subjects, and for developing appropriate preventive measures.

Results from previous studies suggest that survivors of preterm birth are at increased risk of hypertension, stroke, and cardiovascular mortality but not ischemic heart disease (4–8). To the best of our knowledge, the association between preterm birth and risk of heart failure (HF) has not previously been explored. HF in children and young adults is an unusual but dangerous condition with high mortality

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rates (9,10). Congenital heart disease and cardiomyopathies, particularly idiopathic dilated cardiomyopathy, are the main causes of HF at young age (11–13). Incidence data for pediatric HF are scarce but were estimated to be 0.87 per 100,000 person-years in a study in the United Kingdom and Ireland of HF caused by cardiac muscle disease (14). Between 1987 and 2006, the incidence of HF among young adults in Sweden increased by 50%, and the proportion of cardiomyopathies as an underlying cause of HF increased from 15% to 25% (15).

Preterm birth entails exposure of the immature infant heart to extrauterine conditions. Evidence from animal models and small studies of preterm infants shows that preterm birth interferes with normal cardiac development in the neonatal period (16–19). In a cardiac imaging study of adults born preterm, ventricular mass in adulthood was seen to increase with lower gestational age at birth. Preterm birth was also associated with further alterations in cardiac structure and function (20).

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We hypothesized that preterm birth is associated with an increased risk of later HF. In a nationwide Swedish cohort study including >2.6 million live births, we investigated the association between gestational age at birth and risk of incident HF in childhood and young adulthood.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION. This registry-based cohort study included 2,665,542 individuals born in Sweden and registered in the Medical Birth Register between 1987 and 2012 (**Figure 1**). Individuals were followed up from 1 year of age until death, emigration, first diagnosis of HF or ischemic heart disease, or end of study (December 31, 2013), whichever came first. Start of follow-up was set to 1 year of age to avoid measuring HF as an immediate complication during neonatal care.

A unique personal identity number given to all Swedish residents allows for comprehensive cross-linking with other national registries (21). The caregivers are required by law to contribute information to these registries. The Medical Birth Register was started in 1973 and covers >98% of all births in Sweden (22). Since 1982, it is based on copies of standardized clinical record forms used in all antenatal care clinics and delivery and neonatal wards in the country, and it contains data on both mother and infant. The National Patient Register contains data on patient diagnoses and medical and surgical procedures (23). The registry covers all hospitalizations in Sweden from 1987 onward, and information on hospital-based outpatient care is included from 2001. The Cause of Death Register provides information on causes and dates of death in Sweden from 1961 (24). The Multi-Generation Register was created in 2000, and it includes individual index-persons born after 1932 who were alive in 1961 and links them to their parents (25). Information on educational level was collected from the Swedish Register of Education (26). Date of emigration was retrieved from the Register of the Total Population (27).

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HF = heart failure

ICD = International Classification of Diseases

RR = relative risk

EXPOSURES. Data on the main exposure (i.e., gestational age at birth) were retrieved from the Medical Birth Register and categorized into 22 to 27 weeks (extremely preterm), 28 to 31 weeks (very preterm), 32 to 36 weeks (moderately preterm), and ≥37 weeks (term). Since the early 1990s, all pregnant women in Sweden are offered a diagnostic ultrasound scan in the early second trimester, usually between weeks 17 and 20, and >96% accept (28). When no information on ultrasound dating of pregnancy was available, the last menstrual period was used for assessing gestational age.

Data on size at birth were calculated as deviation from the estimated weight for gestational age and sex, based on the Swedish reference curve for intrauterine growth (29). Individuals were categorized as very small (<−2 SD), small (2 SD to <1 SD), appropriate (−1 SD to 1 SD), large (>1 SD to 2 SD) or very large (>2 SD). These data were also used to statistically correct for the possibility that an association between preterm birth and later HF is confounded by low birth weight for gestational age, a proxy for poor fetal growth.

OUTCOMES. The primary outcome was a diagnosis of incident HF without a previous diagnosis of ischemic heart disease in the National Patient Register or the Cause of Death Register. The International Classification of Diseases (ICD)-9th revision (ICD-9; used between 1987 and 1996) and 10 (ICD-10; introduced in 1997) were used to define HF (ICD-9 code 428 and ICD-10 code I50) and ischemic heart disease (ICD-9 codes 410 to 414 and ICD-10 codes I20 to I25).

OTHER VARIABLES. From the Medical Birth Register, we included information on maternal factors such as age at delivery, country of birth, singleton or multiple pregnancy, diagnosis of hypertension, preeclampsia, diabetes mellitus, or gestational diabetes. Data on maternal smoking in the Medical Birth Register were divided into 2 groups according to information collected at the first antenatal visit,