Preterm births (<37 weeks’ gestation) are increasing worldwide and account for 8% of Canadian births.1 With advances in perinatal care over the last 20–30 years, more than 90% of preterm infants survive and enter adulthood.2 The “Barker hypothesis” of fetal origins of adult disease was supported by studies that found associations between low birth weight and adult diseases, such as cardiovascular disease.3 Although those pioneering studies did not distinguish low birth weight due to intrauterine growth restriction in full-term newborns from prematurity, mounting evidence now suggests that preterm birth, above and beyond low birth weight, may lead to hypertension, cardiac dysfunction, obstructive lung disease, glucose intolerance and osteopenia.

There are no guidelines for the long-term medical follow-up of people born preterm. Recently, it was proposed that physicians should enquire about neonatal history throughout the life span, particularly because the risk of premature death is increased by 40% in young adults who were born preterm.4,5 Identifying preterm birth as a risk factor for early-onset chronic disease is critical in implementing preventive strategies and targeted screening to halt disease progression and to avoid premature death.

We review evidence linking preterm birth to adult chronic ailments, focusing mainly on evidence from systematic reviews and observational cohort studies, to provide a guide for physicians providing treatment to adults who were born preterm (Box 1).

Why are young adults born preterm at greater risk of chronic diseases?

Preterm infants are exposed to various sources of injury both in utero and after birth at a time when their organ systems are at a critical stage of development (Figure 1). The fetus or newborn will undergo adaptive mechanisms that may be deleterious in the long-term owing to permanent alterations in organ system development, possibly through epigenetic and genetic mechanisms.6 Moreover, perinatal events could directly cause structural injury through inflammatory processes and abnormal repair.7 In preterm infants, these disturbances induce a phenotype that might heighten their risk for later chronic diseases because of morphologic and functional changes in the infants’ organ systems.

Specific perinatal factors confer additional risk for organ dysfunction, and their presence should be assessed by clinicians: being born to a mother with gestational hypertension or diabetes, intrauterine growth restriction, birth weight of less than 1500 g and prolonged oxygen dependence after birth.5,6

What is the effect of preterm birth on cardiovascular health?

Preterm birth is associated with greater risk of hypertension and changes in cardiovascular structure and function that are typically seen in people at risk of heart failure. A Swedish cohort study involving 674 820 participants documented a 7% higher risk of dying in young adulthood from cardiovascular disease for each week of increased prematurity (hazard ratio 0.93, 95% confidence interval [CI] 0.88–0.99).4 In addition, young adults born very prematurely (<32 weeks’ gestation) from another prospective cohort (n = 1 306 943) showed a 1.89-fold increased hazard of cerebrovascular diseases

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**Key Points**

- Perinatal history is relevant across the lifespan.
- Infants born preterm are at increased risk of hypertension, cardiovascular events, diabetes, chronic pulmonary disease, pregnancy complications and osteoporosis later in life.
- A low threshold for screening for chronic diseases in adults who were preterm infants is warranted because of the increased risks for these patients.

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CMAJ Podcasts: author interview at https://soundcloud.com/cmajpodcasts/150450-rev
compared with peers born at term (95% CI 1.01–3.54).\textsuperscript{8}

Hypertension has consistently been shown to be more prevalent among adults born preterm, with an inverse correlation between systolic blood pressure and gestational age.\textsuperscript{9} Meta-analyses have shown higher resting systolic blood pressure (mean difference [MD] 3.8 mm Hg, 95% CI 2.6 to 5.0 mm Hg) in people born preterm from childhood to young adulthood, along with higher diastolic blood pressure (MD 2.6 mm Hg, 95% CI 1.2 to 4.0 mm Hg) and 24-hour ambulatory systolic blood pressure (MD 3.1 mm Hg, 95% CI 0.3 to 6.0 mm Hg).\textsuperscript{10–12} The effect of prematurity on blood pressure is of particular relevance for women during their reproductive years. In a Canadian population-based study, women who had been born very preterm had a 50% increased risk of gestational hypertension, preeclampsia and chronic hypertension compared with women who had been born at term.\textsuperscript{9}

Structural and functional changes that mediate programing of hypertension and cardiovascular disorders following preterm birth are still unclear but likely involve multiple organ systems including the vasculature and heart, kidneys and sympathetic nervous system.\textsuperscript{13,14} Recent comprehensive vascular phenotyping in people born preterm showed structural macrovascular changes — particularly a narrowing of the aorta — and microvascular dysfunction evident by early adulthood.\textsuperscript{15} These long-term changes may, in part, be driven by coassociated perinatal factors such as maternal hypertension and post-

**Box 1: Evidence used in this review**

We searched PubMed for articles published in English between March 2005 and February 2015 using the medical subject headings “infant, premature” and “infant, low birth weight” in combination with the following key words: “cardiovascular,” “hypertension,” “insulin sensitivity,” “metabolic syndrome,” “pulmonary outcomes,” “osteopenia,” “bone mass,” “adult outcome.” In addition, we reviewed relevant papers identified from the reference lists of retrieved articles. We included systematic reviews and observational cohort studies that compared people born preterm with those born at term as the control groups.

**Figure 1:** Common adverse intrauterine conditions that may trigger preterm birth (e.g., preeclampsia, gestational diabetes, fetal growth restriction and chorioamnionitis) can influence fetal programming. After birth, complications related to prematurity such as sepsis, lung and brain injury, and malnutrition — and their treatments (e.g., oxygen, parenteral nutrition, steroids) — further alter organ system development.
nal interventions rather than preterm birth.16,17

In addition, preterm birth appears to have a
direct effect on myocardial tissue. In a prospec-
tive cohort study, 102 young adults (20–39 yr)
born preterm (mean 30 ± 2 weeks’ gestation) and
132 members of a control group born at term
underwent cardiac magnetic resonance imaging.
Participants born preterm had altered cardiac
shape characterized by increased left and right
ventricular mass and reduced ventricular vol-
umes.18,19 Prolonged neonatal ventilation was a
risk factor for greater right ventricular mass.
Impaired systolic and diastolic function, which
was more pronounced on the right than on the
left side, was also documented: 6 of 102 mem-
bers of the preterm group versus none of the
members of the control group displayed mild
right ventricular systolic dysfunction (ejection
fraction of 42%–45%).

National pediatric organizations currently rec-
ommend annual blood pressure measurement
starting at three years of age to detect early sec-
tary hypertension.20,21 Given the clear associa-
tion between preterm birth and hypertension,
blood pressure should be measured regularly
from childhood to allow for early management
of cardiovascular disease risk. Pregnant women
who were born preterm should undergo careful
blood pressure monitoring. Cardiac and vascular
phenotype may offer a means to stratify a pa-
tient’s risk.

Does preterm birth increase
the risk of metabolic syndrome?

Adverse metabolic changes contributing to risk of
diabetes and cardiovascular events are seen fol-
lowing preterm birth, but results are inconsistent.
A Swedish cohort study involving 630 090 young
adults born in the 1970s with long-term follow-up
at 25–37 years of age showed that people born pre-
term had a 13% increased use of insulin or orally
administered hypoglycemia agents compared with
members of a control group born at term (odds
ratio [OR] 1.13, 95% CI 1.02–1.26).22 Furthermore,
ods of gestational diabetes were much higher in pregnant women who had been born
very prematurely than in those who had been born
at term (OR 2.34, 95% CI 1.65–3.33) in a cohort
study.9 Conversely, a meta-analysis examining
components of the metabolic syndrome found
higher blood pressure and higher fasting low-
density lipoprotein levels in adults born preterm
than in peers born at term, but no difference in
body mass index, fat distribution, fasting glucose,
fasting insulin or levels of high-density lipoprotein
and triglycerides.11 Yet, a recent population-based
cohort study (n = 711) showed that odds of fulfill-
ing the criteria for metabolic syndrome were 3.7
higher (95% CI 1.6–8.2) in young adults who had
been born at less than 34 weeks than in their peers
born at term.23

The link between preterm birth and insulin
sensitivity was the subject of a recent system-
atic review.24 In early childhood, reduced insu-
lin sensitivity was seen following preterm birth,
but as children aged, the strength of this associa-
tion decreased. In three of the studies
reviewed, fat mass was the strongest determi-
nant of insulin sensitivity in young adults born
preterm, but contradictory results were seen in
two other studies in which the effect of preterm
birth persisted irrespective of anthropometric
measures.24 Patients enrolled in published studies
were less than 30 years old, and thus longer
term follow-up will more clearly determine
whether aging interacts with prematurity to
increase risk of metabolic syndrome. Indeed,
comprehensive assessment of glucose homeo-
stasis in more than 100 young adults (aged
18–27 yr) with a birth weight of less than
1500 g (gestational age 24–36 wk) and more
than 100 members of a control group born at
term showed that reduced insulin sensitivity
was compensated for by increased insulin
secretory response. This compensation could,
over time, lead to pancreatic β-cell exhaustion
and the development of diabetes.25,26

The mechanisms leading to abnormal meta-
bolic homeostasis in people born preterm are
complex and remain unclear, but they could
involve nutritional deficits both in utero (particu-
larly in growth-restricted newborns) and after
delivery, where parenteral nutrition given in the
neonatal unit may be insufficient to compensate
for energy demand. Rapid crossing of growth
percentiles for weight without a parallel catch-up
for length may then foster an obesogenic pheno-
type.27,28

Data linking preterm birth to the metabolic
syndrome are insufficient to recommend
screening for type 2 diabetes and dyslipidemia
beyond what is currently suggested by the
Canadian and American diabetes associations.
Primary care physicians may consider preterm
birth along with predisposing conditions, such
as obesity, when determining a patient’s overall
risk of metabolic syndrome.

Are we seeing a new pulmonary
overlapping syndrome?

Young adults born preterm, particularly those
with bronchopulmonary dysplasia (BPD, the
chronic lung disease of prematurity), have impaired respiratory function characterized by persistent and frequent respiratory symptoms, such as chronic cough, dyspnea and wheezing, in addition to signs of airway obstruction. About 10% of adults who were born preterm use bronchodilators and inhaled corticosteroids, compared with 4%–6% of those born at term. Systematic reviews have reported abnormal pulmonary function testing, consistent with airflow limitation in the proximal and more distal airways, among adults born preterm, as evidenced by reduced forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC) and forced mid-expiratory flow. Forced expiratory volume was 0.77 standard deviations (SDs) (95% CI –0.94 to –0.60) lower in young adults who were born preterm than in those born at term, which is equivalent to a 10% decrease in predicted value. Patients with BPD had even greater reductions in FEV₁ compared with those without the disease (MD –0.83 SD, 95% CI –1.01 to –0.64). Unlike in patients with asthma, airflow obstruction was only partially reversible after administration of bronchodilators, with 68%–72% of children with BPD not responding to all such treatment. These results suggest that structural changes originating in the neonatal period may lead to fixed reductions in airway caliber. At the alveolar level, impaired gas transfer has been documented with lower diffusion capacity in patients born preterm. Radiological studies using chest computed tomography have almost universally described abnormal findings, including fibrosis, air trapping and even emphysema, in patients with BPD and in most preterm infants without BPD born at or before 28 weeks’ gestation.

Peak lung growth and function are reached in the 20s before natural age-related decline takes place. Patients with BPD or people born preterm who smoke have a greater decline in the ratio of FEV₁ to FVC between the ages of 8 and 18 years. Concerns exist as to whether preterm birth may predispose the patient to chronic obstructive pulmonary disease. In addition, given the adverse effect of prematurity on vascular development, pulmonary vascular disease such as pulmonary hypertension could emerge as an additional morbidity in adulthood, but this has not yet been investigated.

Patients who were born preterm and who have persistent respiratory symptoms should undergo pulmonary function testing to document airway obstruction and bronchodilator response to guide management. However, evidence is currently lacking regarding the best therapeutic strategy.

Is normal peak bone mass achieved in adults born preterm?

Failure to achieve peak bone mass following prematurity with subsequent increased risk of osteoporosis is a concern, given that 80% of bone mineral accretion occurs during the last gestational trimester. Furthermore, preterm infants experience nutritional deficits during the neonatal period in addition to prolonged immobilization and exposure to calcium-wasting medication. Yet, studies on long-term bone health in patients born preterm are scarce, and their results are equivocal. In a Finnish observational cohort study, dual energy X-ray absorptiometry was performed to examine bone mineral density. Low bone density (z score ≤ –1 unit) was detected in 44% of the 144 young adults born preterm and in 26% of the 139 members of the at-term control group, representing a 2.3-fold increased odds (95% CI 1.4–3.8). In contrast, gestational age was not related to bone density in two other well-designed prospective cohort studies. However, participants in those studies were born less prematurely (30–35 wk) and were relatively healthy in the neonatal period, which suggests a possible threshold in gestational age below which prematurity-related medical complications may interfere permanently with bone development.

Given the potential increased risk of low bone density and possible subsequent fractures, adults who were born preterm should be reminded to eat a calcium-rich diet and engage in weight bearing activities.

Conclusion

A substantial proportion of current youth and adults were born preterm. This population is at increased risk of developing chronic health problems. Most problems are pulmonary. Cardiovascular and metabolic problems may also occur and, in women, may become most evident during pregnancy. Early detection of risk factors and subclinical disease states in patients who were born prematurely is critical to mitigating undesirable health events. It is our role as clini-

Box 2: Unanswered questions

- Are signs and symptoms of chronic adult ailments the result of a static injury during the neonatal period (arrested development) or a progressive disease triggered by preterm birth?
- What interventions can prevent these adverse outcomes during the neonatal period and beyond?
- Is preterm birth the surrogate marker for maternal disease, which may be the key determinant of adult health?
cians to identify patients at risk by enquiring about perinatal history to the same extent that we ask about smoking or family history of early cardiovascular death.

Future studies should examine the mechanisms that induce changes in organ structure and function following preterm birth, to identify targets for early interventions, improvements in perinatal practices and pharmacologic or behavioral modalities that could improve overall health outcomes (Box 2).

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