Chronic Kidney Disease in Disadvantaged Populations

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Chapter 23

Prematurity, Low Birth Weight, and CKD

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Chapter Outline

The global burden of chronic diseases, including chronic kidney disease (CKD), is increasing with changing mortality rates, population growth, increased longevity, and lifestyle changes. There is also increasing awareness of the influence of early life factors, including impaired intrauterine growth and abbreviated gestation, which is central to this discussion.

1 CHRONIC KIDNEY DISEASE

The development and progression of CKD can be interpreted in a life course theory framework, accommodating multideterminant disease models, and incorporating newer concepts of acute kidney injury (AKI). The burden of CKD in a population is also influenced by longevity and by competing causes of mortality.

CKD is the precursor of most cases of terminal kidney failure and is also associated with premature nonrenal death. Terminal kidney failure is a death sentence in countries without universal access to renal replacement therapy (RRT). Provision of RRT to suitable candidates in many affluent countries extends an individual's survival by a limited number of years, although often with poor quality of life, and RRT poses an increasing burden on health services, with costs that might soon be unsupportable.

Optimal development of the kidney depends on both a favorable intrauterine environment and a full term gestation. Nephron development is completed by the 36th week of gestation, with establishment of the nephron complement that must then carry an individual throughout life [1]. Nephrons are lost at various rates throughout life, reflecting age-related changes, as well as variably superimposed nephropathic processes. Kidney function at any time depends on the balance between original nephron endowment and loss of nephrons to that point; CKD is diagnosed when abnormalities in kidney function or structure are detected, and renal insufficiency is diagnosed when residual kidney function can no longer maintain a minimally symptomatic state. This can only occur in people who have escaped other causes of death to that point [2]. CKD progresses with age, so that increased burdens of CKD will be inevitable in developing countries as other causes of premature mortality are reduced, and life expectancy is increased [2].

Multideterminant models [3,4] can accommodate considerations of both kidney development and kidney injury and compromise throughout the life course. In disadvantaged populations, suboptimal kidney development is common, reflecting an adverse intrauterine environment and/or an abbreviated pregnancy, as discussed in subsequent sections. In addition, disadvantaged populations are generally exposed to an excess of postnatal "nephropathic" risk factors, which can operate sequentially or simultaneously over the life course, and have summed or multiplicative effects in propagating loss of kidney function.

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Many nephropathic insults are now considered as episodes of AKI [5]. There is increasing recognition of the cumulative end-organ effects of multiple episodes of AKI and acknowledgment of the mutual relationships of AKI and CKD.

Many causes of AKI are common in disadvantaged populations [6–10]. They include hypotension, hypoxemia, volume contraction, dehydration, heat stress, inflammation, infections, run-of-the mill infections and sepsis, infections due to region-specific diseases (malaria, dengue, HIV, leptospirosis, Ebola, etc.), injuries, obstetric calamities, rhabdomyolysis, envenomations. They include toxicities from unregulated mainstream medicines, such as analgesics, antibiotics, lithium, contrast and chemotherapeutic agents. Time- or treatment-limited episodes of glomerulonephritis, interstitial nephritis and vasculitis also qualify as AKI events, as do occurrences of urinary tract infection and urinary obstruction. Disadvantaged population is often confounded with malnutrition.. Harmful physical exposures through poorly regulated work practices, and through ecosystem contamination with toxic heavy metals, fertilizers, herbicides, pesticides and their adjuvants, vehicles, contaminants, and breakdown products can also contribute to kidney injury, although effects are both acute and chronic [11,12]. Furthermore, as people age, the more chronic effects of obesity, the metabolic syndrome, diabetes, hypertension, and arteriosclerosis are increasingly likely to be superimposed. Against this high risk background, high levels of stress are likely and quality health services are usually unavailable.

2 INEQUALITIES AROUND THE WORLD: LBW, PREMATURITY AND THE HUMAN DEVELOPMENT INDEX (HDI)

The Human Development Index (HDI) is a composite measure of life expectancy, education, and per capita income, and is one of several indicators used to gauge welfare of population, or potentially, quality of life [13,14]. Global rankings are by individual values (Fig. 23.1A) against a standard of 1.0, and in four broad categories of low, <0.550; medium, 0.550–0.696; high, 0.697–0.8; and very high, >0.801 [15]. HDI improved in most countries from 1990 to 2014, but great disparities remain. Measures which are correlated inversely with HDI include infant mortality, maternal mortality, and impaired childhood growth, or stunting [13,14], as well as the proportions of the population living in poverty, proportions in vulnerable employment, and depth of the food deficit (the gap between needed and actual caloric intake), while public health expenditures are lowest in the low HDI countries. Fertility rates per woman are higher in low HDI countries, and so too is gender inequality. Gender inequality is a composite measure derived from proportions of babies born to adolescents, from maternal mortality rates, proportions of girls/women with some secondary education, work force participation, and political representation by women. It is a critical measure of the status of women, which reflects strongly on reproductive health.

Two vital gestational outcomes, the proportion of babies born with low birth weight (LBW) and proportions born prematurely, are also inversely correlated with the HDI, as shown in Fig. 23.1B–C [16–18]. These are strong indicators of maternal health and well-being before conception, as well as the course and characteristics of pregnancies themselves. For the fetus they are powerful predictors of postnatal health status and early life mortality, and are also determinants of health and mortality risk in adult life. Some recent data on LBW and prematurity are shown in Box 23.1 [17,18].

3 CAUSES OF LOW BIRTH WEIGHT AND PRETERM BIRTH

In developing countries, LBW and preterm birth are very often linked: most LBW is associated with preterm births, and many growth-restricted babies are born preterm. In affluent countries however, lower rates of LBW and prematurity are not always linked. While premature births produce LBW babies, some causes of premature labor can precipitate birth of a baby that is not growth restricted in relation to gestational age [19–21].

The World Health Organisation (WHO) has produced, from metaanalysis of 895 studies, a summary of factors linked to birth weight, gestational age, prematurity, and intrauterine growth retardation (IUGR) [22]. The report states that "*well established direct causal impacts on intrauterine growth include, (beyond infant sex), racial/ethnic origin, maternal height, prepregnancy weight, paternal weight and height, maternal birth weight, parity, history of prior low birth weight infants, gestational weight gain and caloric intake, general morbidity and episodic illness, malaria, cigarette smoking, alcohol consumption, and tobacco chewing. In developing countries, the major determinants of IUGR are Black or Indian racial origin, poor gestational nutrition, low prepregnancy weight, short maternal stature, and malaria. In developed countries, the most important single factor, by far, is cigarette smoking, followed by poor gestational nutrition, and low prepregnancy weight. In relationship to abbreviated gestation (preterm birth), only prepregnancy weight, prior history of prematurity or spontaneous abortion, in utero exposure to diethylstilbestrol, and cigarette smoking have well established causal effects, and the majority of prematurity occurring in both developing and developed country settings remains unexplained.*" Additional reports cite, as reasons for poor fetal growth, extremes of maternal age (<20 years and >45 years), closely spaced pregnancy, macro- and micronutrient deficiency, alcohol use, second-hand smoke, inflammation, maternal infections, vaginosis, chorioamnionitis, intrauterine hypoxia, eclampsia and preeclampsia, as well as stress, exhaustion, abuse,

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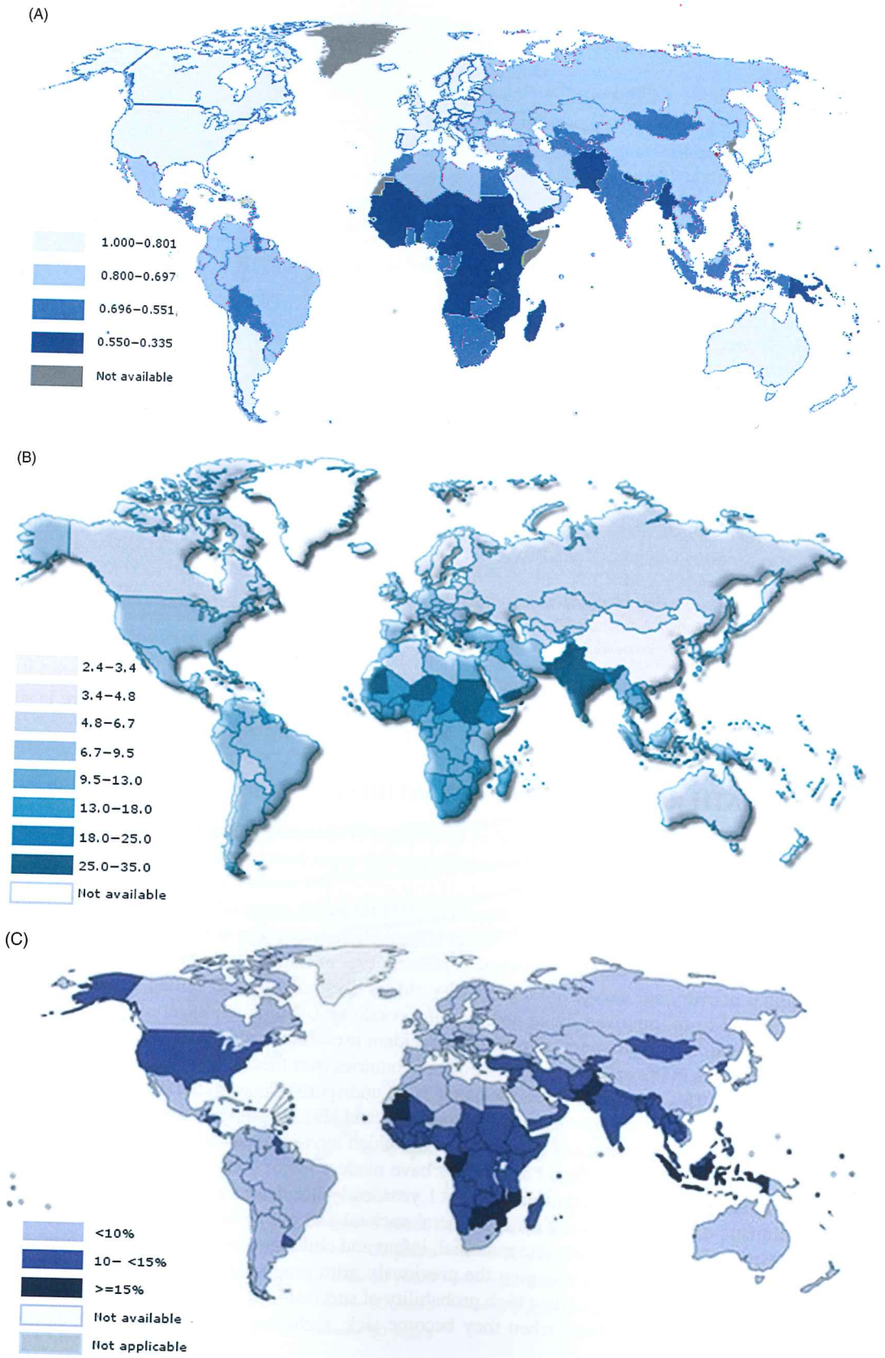

FIGURE 23.1 (A) Human Development Index, 2013. (B) Low birth weight %, 2014. (C) Preterm birth rate per 100 live births, 2010. *(Part A: Adapted from United Nations Development Program, 2014* and Wikimedia, 2014 *[13,15]; Part B: Adapted from index mundi, 2015 [16]; Part C: Adapted from March of Dimes, 2012 [17].)*

BOX 23.1 LBW [18] and Preterm Birth [17]

Definitions

LBW: <2500 g
Very LBW: <1500 g
Prematurity: gestation <37 weeks
Moderate prematurity: gestation 28 to <37 weeks
Severe prematurity: gestation <28 weeks

Points to note.

- LBW and preterm birth are closely associated and share many risk factors
- Birth weight is measured in only about 60% of births globally, and in smaller proportions in Africa and India
- In 2000, about 20.7 million babies worldwide were LBW
- 95% of LBW babies were born in developing countries
- Most were born in SE Asia (>40 million in India) and Africa
- Most LBW babies are also premature, <37 weeks, but other factors can generate LBW in term babies
- Recent rates of LBW ranged from 3% to 32%
- Rates did not change much globally from 1990 to mid-2000s
- Gestational age is recorded less frequently than birth weight
- At least 15 million preterm births are recorded each year
- More than 60% of preterm births occur in South Asia and sub-Saharan Africa
- Fifteen countries account for 66% of the world's preterm births. In descending order they are: India, China, Nigeria, Pakistan, Indonesia, USA, Bangladesh, Philippines, Dem Rep of Congo, Brazil, Ethiopia, United Republic of Tanzania, Uganda, Sudan, and Kenya
- Rates of preterm birth are increasing in almost every country in which it is measured

violence, and poverty [16,23,24]. The extent to which effects of poverty and disadvantage are mediated through other factors, needs ongoing study. Absent or deficient health services are also implicated. Furthermore, there is significant intergenerational correlation of birth weight, which might be only partly environmental [25].

4 CHANGING DEATH RATES AROUND THE WORLD

The increase in chronic disease needs to be understood in the context of changing mortality; reductions in infant and childhood deaths result in expansion of the adult population, and longer life expectancy among adults increases the numbers and proportions susceptible to chronic disease.

Over the last 100–150 years there has been an astonishing increase in life expectancy at birth, which, for millenia previously, had been relatively stable at <30 years (Fig. 23.2) [26]. Although it began at somewhat different times, increase in life expectancy has occurred in all countries, continues steadily except in times of war, famine, epidemics, and major catastrophes, and applies at every age except among the very old, as illustrated for the United Kingdom in Fig. 23.3 [27]. These changes have flowed from improved living and working conditions, sanitation, water supply, nutrition, and education, as well as from prevention and treatment of infections, accident prevention, and better chronic disease management.

Fig. 23.4 shows the changes in life expectancy in a sample of countries over the last 53 years, and the current approximate disparities among them [28]. This increase in life expectancy is an undisputed triumph, but it poses challenges, not only in resource depletion, crowding, pollution, environmental degradation, and climate change, but also with problems of progressive ageing. Among these, is a greater burden of chronic diseases, which increases with advancing age, and includes CKD.

Dramatic reductions in infant and childhood death rates have made a major contribution to these changes (Fig. 23.5) [29]. The reductions in early life deaths (infant deaths at <1 year, early life deaths at <5 years) in recent years have exceeded the most optimistic expectations. They reflect general societal and public health improvements, better education of girls and women, targeted programs to promote maternal, infant and childhood health, and altered mothering practices, including "kangaroo mothering," which is changing the previously grim prognosis of significantly LBW and premature babies (<32 weeks) in low income settings into a high probability of survival [30]. The fall in infant mortality also reflects better treatment and resuscitation of infants when they become sick, including interventions, such as oral rehydration therapy, antibiotics, and hospital care.

However, rates of LBW and prematurity have been more resistant to change than early life mortality and have actually deteriorated in some settings (Figs 23.6 and 23.7) [31,32]. As discussed later, these will influence health and chronic disease profiles.

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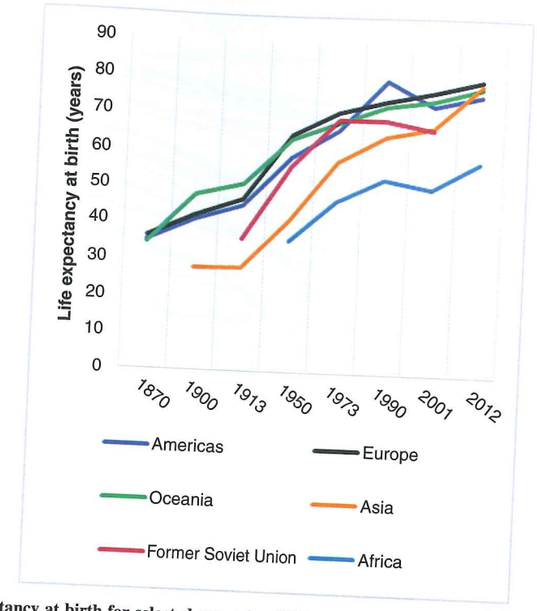


FIGURE 23.2 Trends in life expectancy at birth for selected countries, 1870–2011. *(Adapted from Roser M. Life Expectancy, 1543–2011. http://creativecommons.org/licenses/by-sa/4.0/deed.en_US, 2016. Available from: http://ourworldindata.org/data/population-growth-vital-statistics/life-expectancy/ [26].)*

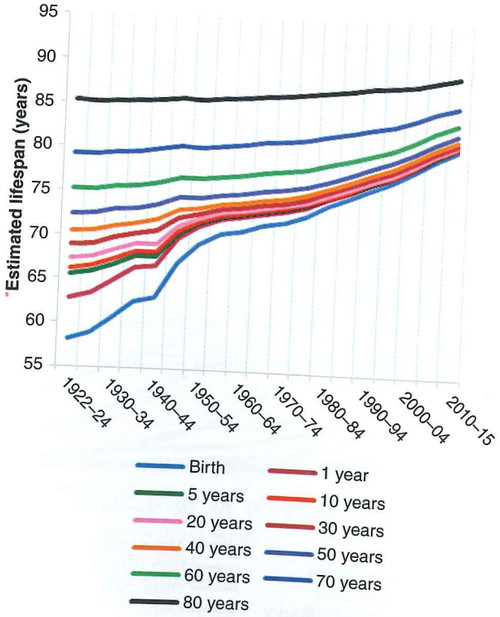


FIGURE 23.3 Estimated lifespan at a range of ages, United Kingdom, 1922–2015. *(Adapted from Human Mortality Database, 2007 [27], source notes: UNITED KINGDOM, DATA SOURCES Last Modified: 2-Sept-2015 1. England & Wales Total Population http://www.mortality.org/hmd/GBRTENW/DOCS/ref.pdf 2. England & Wales Civilian Population http://www.mortality.org/hmd/GBRCENW/DOCS/ref.pdf 3. Scotland http://www.mortality.org/hmd/GBR_SCO/DOCS/ref.pdf 4. Northern Ireland http://www.mortality.org/hmd/GBR_NIR/DOCS/ref.pdf.)*

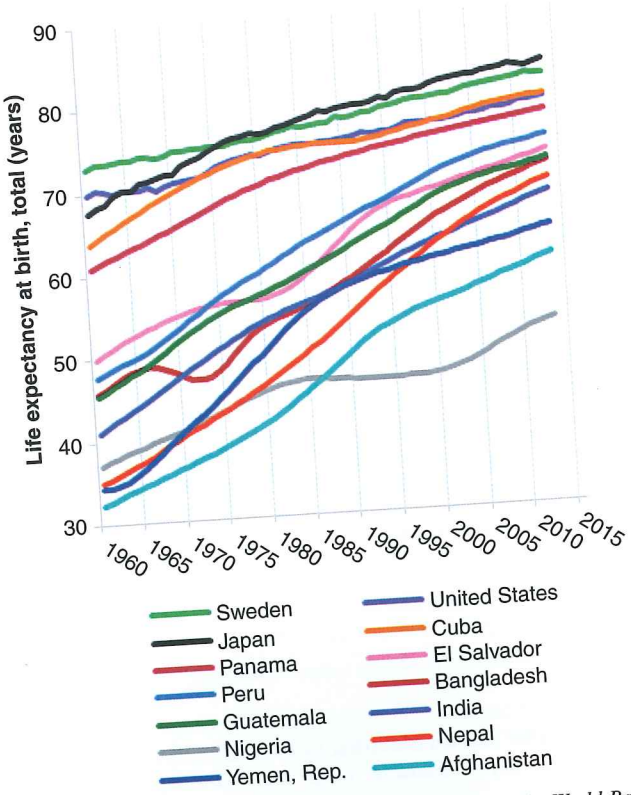


FIGURE 23.4 Life expectancy at birth for selected countries, 1960–2013. *(Adapted from The World Bank, 2016 [28], source notes: derived from male and female life expectancy at birth from sources, such as: (1) United Nations Population Division. World Population Prospects, (2) United Nations Statistical Division. Population and Vital Statistics Report (various years), (3) Census reports and other statistical publications from national statistical offices, (4) Eurostat: Demographic Statistics, (5) Secretariat of the Pacific Community: Statistics and Demography Programme, and (6) U.S. Census Bureau: International Database.)*

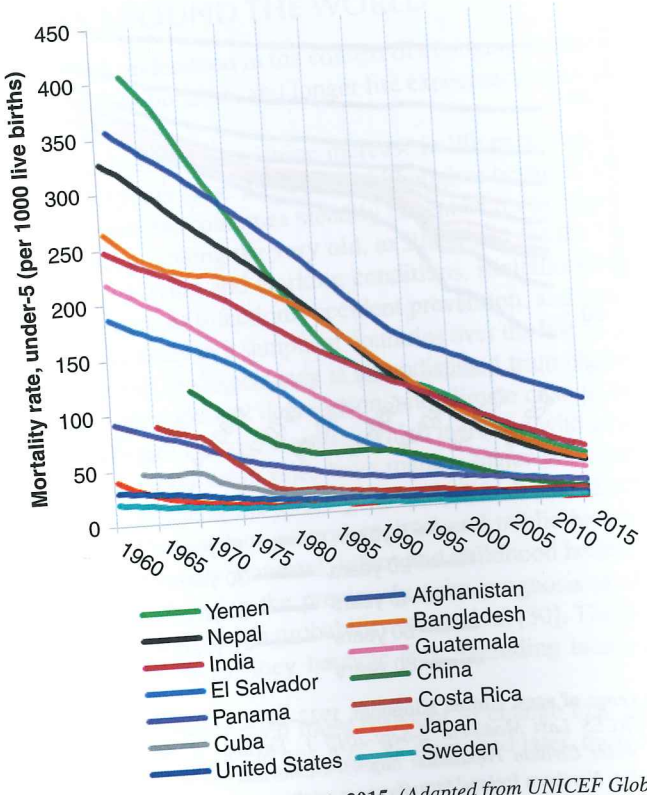
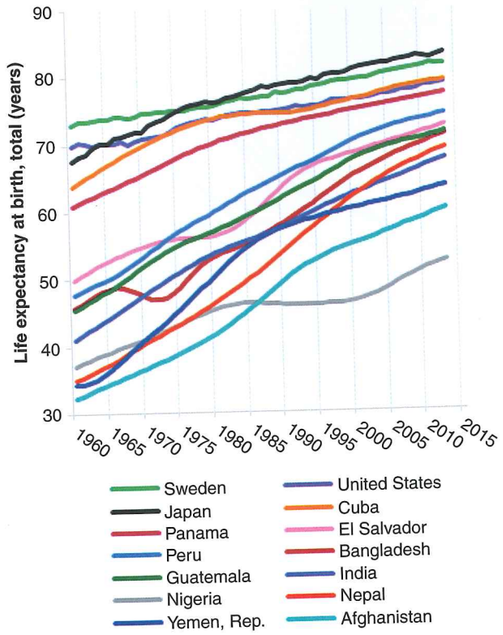


FIGURE 23.5 Under-five mortality rates for selected countries, 1960–2015. *(Adapted from UNICEF Global Database, 2015 [29].)*



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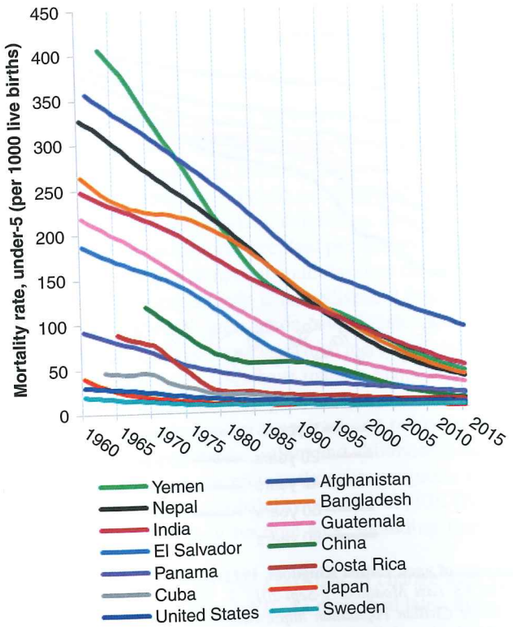

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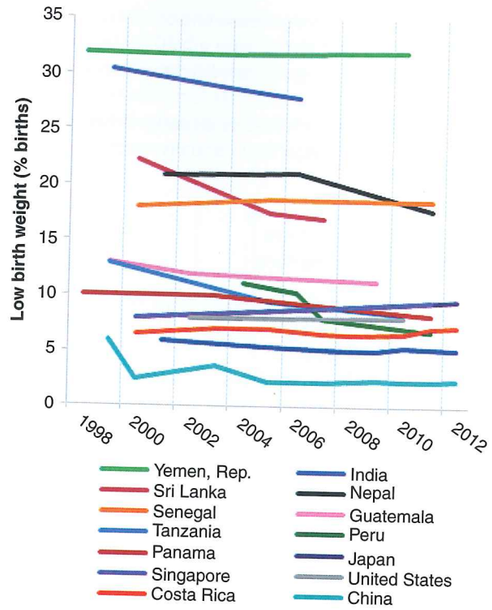

FIGURE 23.6 Low birth weight (LBW) for selected countries, 1998–2012. *(Adapted from The World Bank, 2015 [31].)*

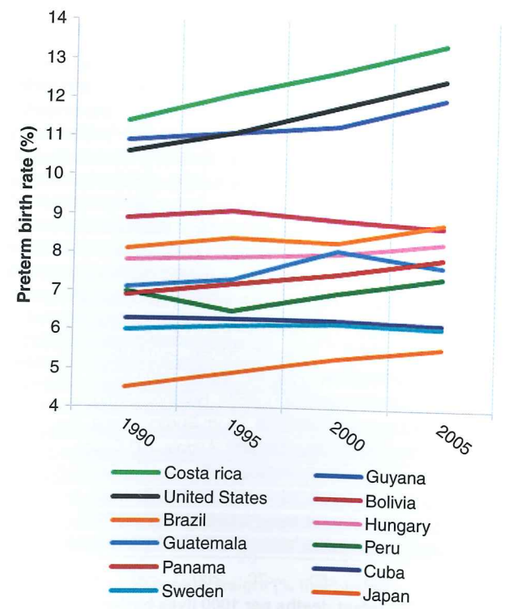

FIGURE 23.7 Preterm birth rate for selected countries, 1990–2005. *(Adapted from Blencowe H, Cousens S, Oestergaard MZ, et al. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Supplementary web tables 18a–d: estimated time trends in preterm birth rates for 65 countries. Lancet 2012;379:2162–72 [32].)*

Reductions in infant and childhood deaths have been almost universal, but there are still marked differences among countries, as shown for infant mortality in Fig. 23.8 [29,33], with a >50 fold range between the highest and lowest rates. Thus, while most children worldwide are now surviving to adult life there is considerable scope for further improvement in many countries.

Variation in rates of LBW are likewise striking, with >14-fold disparity between the countries with the lowest and highest rates (Fig. 23.9) [18,34,35]. However, as noted, rates of LBW and prematurity have been more resistant to improvement

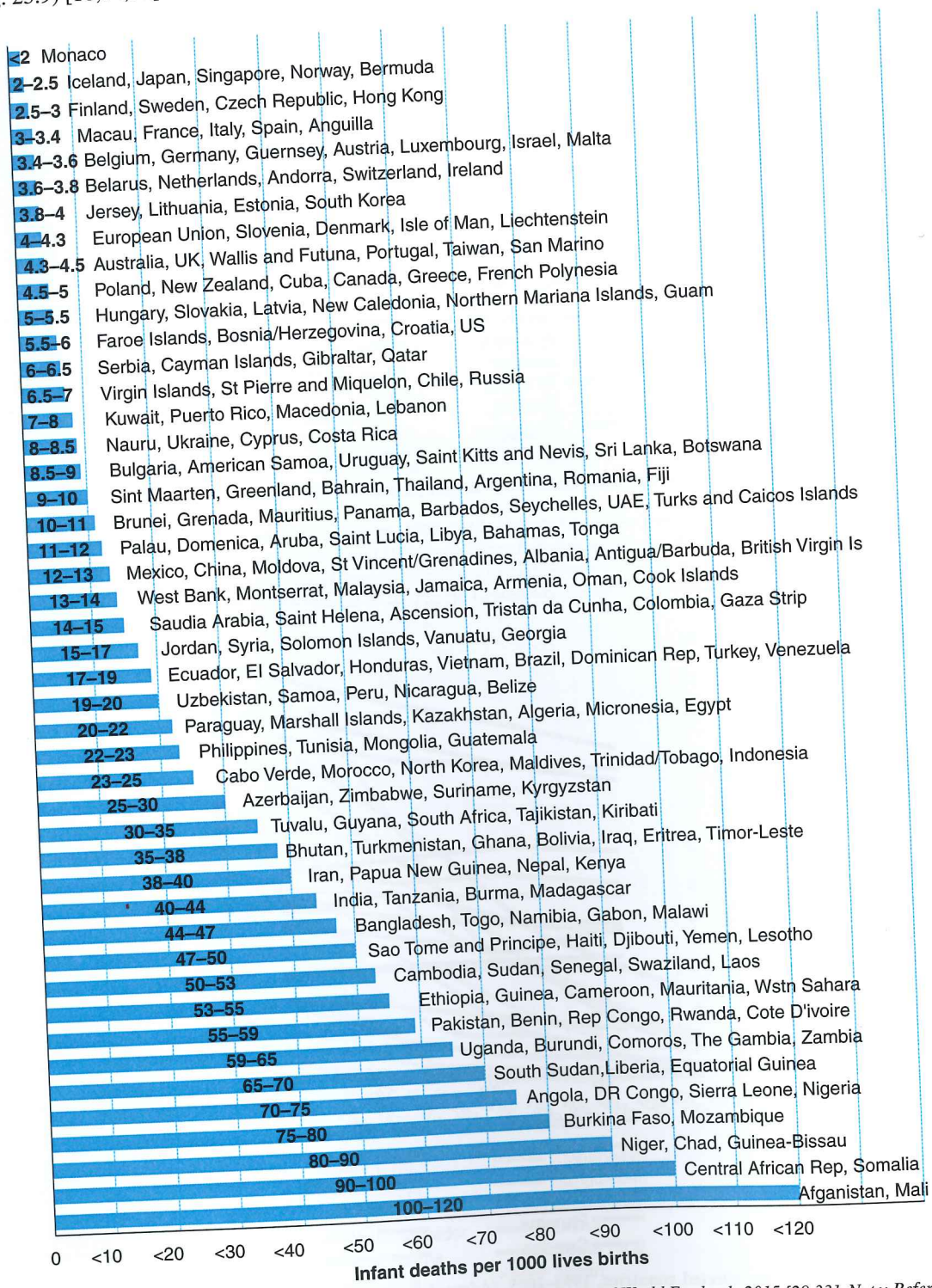

FIGURE 23.8 Infant mortality worldwide. *(Adapted from UNICEF Global Database and World Factbook, 2015 [29,33]. Note: Reference year 2015.)*

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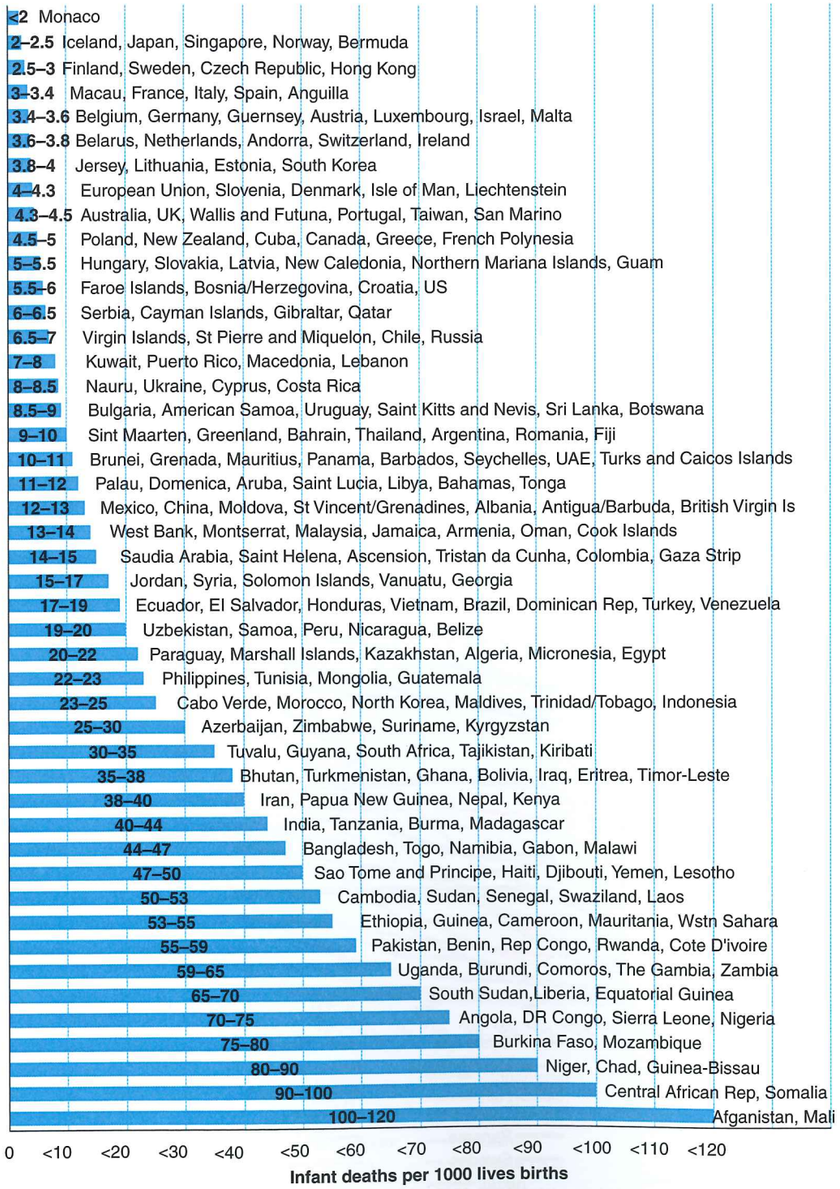

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in many countries, and have actually deteriorated in some settings. In disadvantaged settings, this probably flags the complex sociologic and multigenerational nature of risk for poor gestational outcomes, which are entrenched in poverty, disadvantage, poor education and nutrition, and which better antenatal care can only marginally mitigate. Changing maternal characteristics also contribute, with increased maternal ages at pregnancy, smoking, drinking, drug use, weight gain, and increased age invoked in some settings. Fetal alcohol effect is probably rising in many environments. In addition, in affluent countries, assisted reproduction is producing more multiplex pregnancies. Meanwhile, survivals to discharge of very

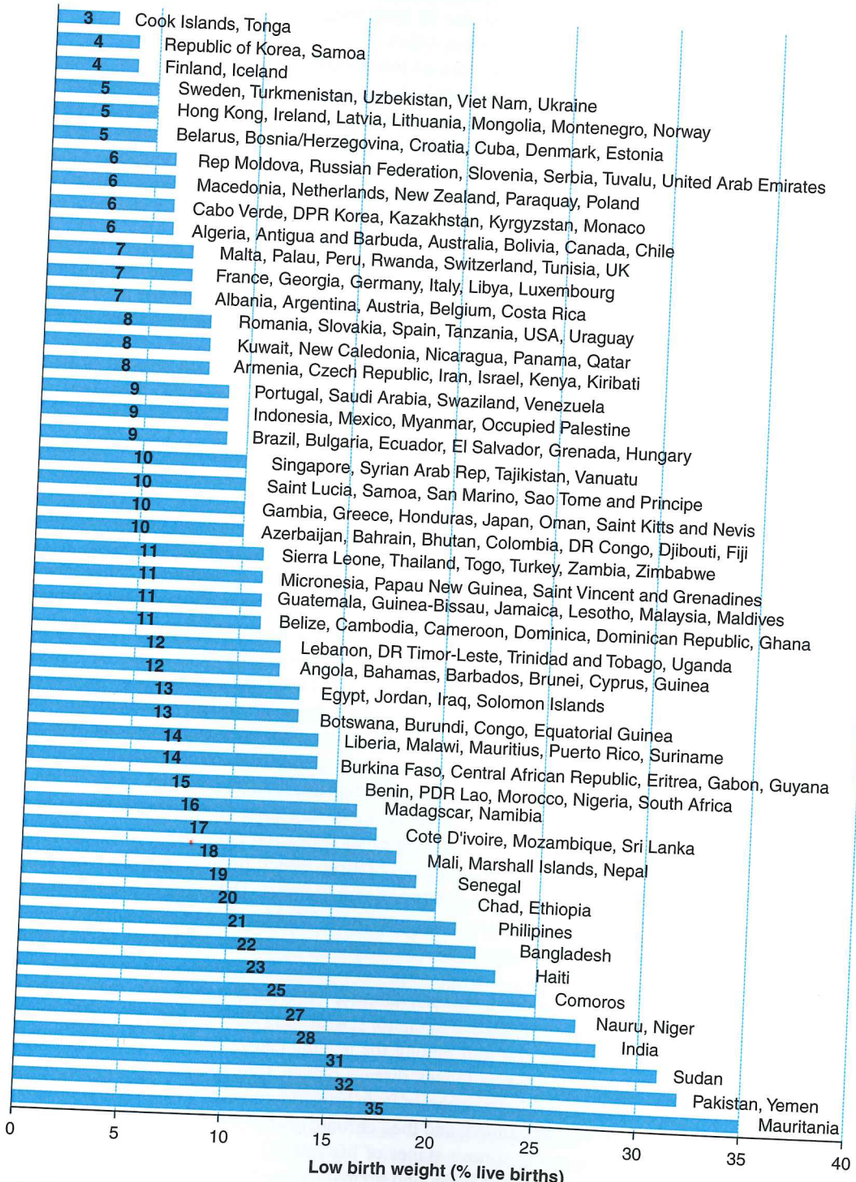

FIGURE 23.9 Incidence of LBW (<2.5 kg) worldwide. *(Adapted from UNICEF Global Databases, 2009–2013 reference years, 2014, UNICEF Improving Child Nutrition, 2007–2011 reference years, 2013, UNICEF Low Birthweight, 1997–1999 reference years, 2004 [18,34,35].)*

LBW and very premature babies are increasing; in many settings 80%–90% of babies born at 26 weeks, and 64% of those of birth weight from 500 to 600 gm are surviving to discharge [24].

5 POSTNATAL HEALTH IN RELATION TO LBW AND PREMATURITY

The postnatal health of these vast waves of infant and children now surviving to adult life is shaped not only by their increasing age, and features of their postnatal environment, but also by birth weight and prematurity profiles. As noted, these have not improved over time as rapidly as early life mortality has fallen.

Forsdahl was the first to document, in Finnmark, that those of lower birth weight have accentuated susceptibility to chronic disease and premature natural deaths as adults [36]; this was later confirmed by Barker et al. [37] and subsequently supported by much other data. The phenomenon has been described specifically for cardiovascular disease, hypertension, type 2 diabetes, the metabolic syndrome, lung disease, liver disease, and more recently, for CKD [38–40]. This heightened risk is also manifest through broader sets of symptoms and syndromes [41]. Research is defining common pathophysiologic mechanisms, common developmental pathways, common critical time periods for several organ systems, and common markers and mediators of deficits associated with LBW and preterm birth [42–44].

Johnson and Schoeni [41] found, in a US cohort born between 1951 and 1969, that both LBW and socioeconomic status (SES) strongly and independently predicted poor health as recorded through a questionnaire and reflecting a wide variety of conditions, at ages 39 to 58 years. They noted that the birth weight effect persisted after accounting for household, neighborhood, number of siblings, and SES.

Power et al. in a commanding review [45], presented insights from a follow up of birth cohorts in Britain (at least seven cohorts), Scotland, Ireland, Norway, Denmark, Europe (EUroCONET), the Netherlands, New Zealand, Australia, and the Pacific. They confirmed the influence of birth weight, and discussed concepts, such as timing, critical periods, programming, and various models (e.g., "chain of events models vs. accumulation of risk models"). They emphasize that socioeconomic position (updated terminology) in both early life and in adult life, have separate impacts on various clinical parameters.

Defreitas et al. [46], note the negative impact of prematurity on organs formed through branching morphogenesis. These include, the kidneys, the lungs' vasculature, mammary glands, and endocrine organs, such as the pancreas. They all have a similar critical period for development, which, like the nephrons, is limited to intrauterine life, maximized in the last trimester, and is interrupted by premature delivery. They note that elastin, which imparts elasticity to the vascular tree, is laid down during angiogenesis in utero, and that its production after birth is negligible, Elastin that is not formed, or is lost prematurely, is replaced by collagen and fibrosis, imparting a premature stiffness to the macrovessels. Myocardial and ventricular hypertrophy is compromised. Development of microvessels or capillaries is similarly timed and is compromised by preterm birth, with decreased density, termed "rarefaction," leading to retinopathy and insulin resistance. They note that premature birth is associated with endothelial dysfunction, and impaired vascular remodeling, as confirmed by Visentin [43], which is linked to hypertension, hyperglycemia, and dyslipidemia, and dysregulation of immune responses, inflammation, capillary integrity, hemostasis, and coagulation. Subclinical indicators of endothelial dysfunction are inflammatory markers, including high C reactive protein, hyperuricemia, and proteinuria. They too, cite the harmful effects of premature rapid transition from a low resistance, low pressure, placental circulation to a high flow, high resistance systemic circulation, which notably impairs ventricular modeling and hypertrophy, as well as impairing lung function and compromising kidneys. They allude to the various biomarkers which flag compromise associated with prematurity (beta trace protein, NGAL, ADMA, etc.). They describe *preterm birth as precipitating a form of premature senescence and note that the shortened telomeres in people born significantly preterm are compatible with this view.*

While the effects of LBW and prematurity on cardiovascular disease, hypertension, diabetes, the metabolic syndrome, liver disease, and potentially CKD, are now clear, their associations with lung disease are especially marked. Chronic obstructive lung disease is ranked between three and four among the leading causes of death globally, and deaths due to respiratory infections also rank very high [47], whereas kidney disease ranked 18th as a cause of death in 2010 [48]. The manifestations of LBW and prematurity on lung disease progress from bronchopulmonary dysplasia in infants and children through respiratory infections, respiratory failure, asthma, and then chronic obstructive lung disease in adults [49], and are influenced by a variety of environmental factors at various stages of life [50,51]. Researchers have developed a plausible scheme for expression of lung disease in the context of LBW and prematurity across the life course, which the renal community might well attempt to emulate [50].

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6 IMPAIRED KIDNEY DEVELOPMENT IN THE CONTEXT OF LBW AND PREMATURITY AND CKD

LBW and preterm birth, are associated with impaired kidney development. This is reflected in lower nephron numbers and in reduced numbers of arcades of glomeruli in the renal cortex. Among the 10-fold variation in nephron numbers (glomeruli) defined in kidneys of people with apparently normal kidney function [51], there is a clear correlation of glomerular numbers with birth weight [52]. LBW and prematurity probably compromise kidney development through mechanisms beyond their influence on nephron endowment, such as impaired vascular supply and reactivity, inflammation, excessive levels of oxidative stress, and impaired energy pathways. When babies are born seriously preterm, kidney development does not complete its normal trajectory in the extrauterine environment. The period of nephrogenesis is abbreviated, some glomeruli, which are formed ex-utero are morphologically abnormal, and markers of tubular compromise or injury are elevated in babies who survive. Furthermore, when prematurely disconnected from the maternal circulation, those immature kidneys are suddenly exposed, weeks too early, to high hydrostatic and vascular pressures, high rates of glomerular filtration, and imperatives for the energy-intensive processes of tubular water and solute reabsorption, for which it is not yet prepared. The seriously premature, growth-restricted baby also experiences many nephropathic factors in the neonatal course, including further hypoxemia, acidosis, hypoglycemia, jaundice, and nephrotoxic antibiotics. These matters are addressed in excellent existing reviews, and research is ongoing [10,42,53–57].

Lung development follows a similar trajectory to kidney development. Development of the airways occurs by branching morphogenesis, is completed by the 36th week of gestation and is especially impaired by deficiency of some micronutrients, such as vitamin A. Furthermore, it is compromised by premature changes in circulation and requirements for oxygenation for which the lungs are not yet matured, and they are further injured by treatments to support oxygenation and survival in the premature neonatal course [50].

The susceptibility of LBW and premature infants to CKD applies across the life course, affecting neonates, children, and adults [42]. Its manifestations potentially depend on the degree of renal developmental restriction. *Severe restriction* might be associated with structural developmental abnormalities, such as aplasia, hypoplasia, single kidney, etc., suggesting a continuum with some congenital abnormalities of the kidneys and urinary tract (CAKUT) syndromes., Kidney histology in some CAKUT syndromes suggests deficiency of nephrons (glomeruli). Severe restriction can also predispose to AKI in the postnatal course, as well as early life renal insufficiency, especially with superimposed adiposity [57,58]. *Serious restriction* could be associated with focal and segmental glomerulosclerosis (FSGS) and proteinuric syndromes in childhood and adolescence. *Moderate restriction* might be manifest through accelerated development of CKD and renal failure in early adult life, often associated with some "specific" morphologic changes (primary FSGS, secondary FSGS, IgA nephropathy, IgM nephropathy, reflux nephropathy, some diabetic changes, etc.). *Mild restriction* might be associated with accentuated susceptibility to the usual forms of CKD associated with advancing age.

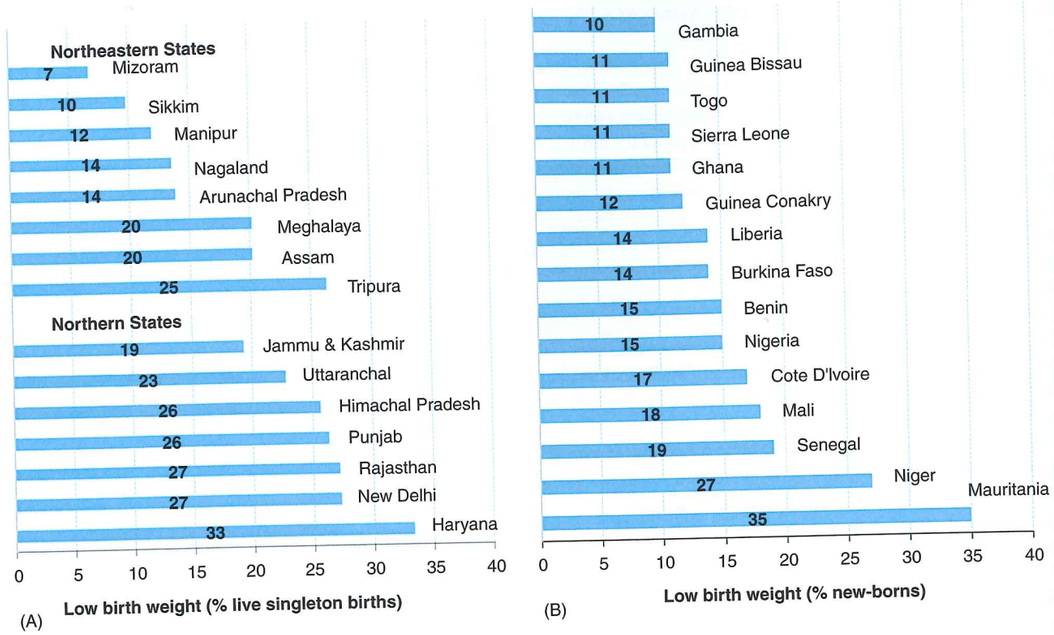
Reports in the last 18 years have described various manifestations of the association of renal disease with LBW in a variety of populations [39,59–71]. Some of these are summarized in previous reviews [1,40]. The CKD markers or outcomes have been variously albuminuria, lower eGFR, more advanced stages of established disease, faster progression of CKD, less frequent or less persistent remissions in subjects treated for specific renal diseases, and the need for RRT. The phenomenon has been described in population-based cohorts followed from birth, in subjects with type 1 diabetes, in IgA nephropathy, in membranous GN, in FSGN, and in a variety of other conditions. It is noteworthy that birth weights, or early determinants, have not yet been seriously considered as facilitators, in the multideterminant context, of the disastrous problem of CKD of unknown etiology (CKDu) among laborers in several regions, including Central America and Sri Lanka [11,12], although the timing of their health transitions and their nutritional circumstances are compatible with a contribution.

Although hypertension and type 2 diabetes are also negatively influenced by LBW and prematurity, the associations of LBW with CKD are not principally mediated through these conditions. CKD in young Aboriginal adults, flagged by albuminuria, is not mediated through those conditions [38], although they are often superimposed later in life. Furthermore, in a study of adults aged 60–64 years in the United Kingdom, Silverwood and coworkers concluded that the causal pathway between birth weight, inversely, and CKD was independent of diabetes and hypertension [72].

7 DISADVANTAGED GROUPS WITHIN COUNTRIES AND REGIONS

In addition to variation in rates of LBW by country, there is often marked heterogeneity in the proportions of LBW births by ethnicity or location within countries and regions. Examples are shown in Fig. 23.10 [34,73–75]. In the United States, African Americans have almost double the rates of LBW than Whites, while Mexicans and Central and South Americans have the lowest rates [73]. In two districts of the Czech Republic, the Roma population has over 4 times as many LBW

FIGURE 23.10 LBW within selected countries or regions by state or ethnicity. (A). India, (B) West Africa, (C) Canada, (D) United States of America. *(Part A: Adapted from Bharati P, Pal M, Bandyopadhyay M, Bhakta A, Chakraborty S, Bharati P. Prevalence and causes of low birth weight in India. Malaysian J Nutn 2011;17(3):301–13. 2005–2006 data; Part B, From UNICEF Global Databases. Low birthweight: Percentage of infants weighing less than 2,500 grams at birth, 2014; 2016. Available from: http://data.unicef.org/nutrition/low-birthweight.html, 2009–2011 reference years; Part C, From Zipursky AR, Park AL, Urquia ML, Creatore MI, Ray JG. Influence of paternal and maternal ethnicity and ethnic enclaves on newborn weight. J Epidemiol Community Health 2014;68:942–49. 2002–2009 data; Part D, From National Center for Health Statistics. Health, United States, 2014; 2016: With Special Feature on Adults Aged 55–64. Hyattsville, MD, 2015. Available from: http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_01.pdf, 2013 data [34,73–75].)*



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births as the non-Roma population [76]. Among the 15 countries of mainland West Africa, there is a threefold range [34]. There is a fivefold range in rates of LBW among the 29 states of India, as well as marked differences by state in regions, with the highest average rate (the Northern Region) and lowest average rates (the Northeastern Region), as shown in Fig. 23.10A [75]. A number of hypotheses have been advanced for these disparities. Low SES, poor maternal, and prenatal health and poor access to prenatal care are important, although there is a growing consensus that they do not fully account for the phenomena [77–80]. High levels of women's economic and social autonomy, as well as literacy, are recognised as important protective factors in the northeast of India [75].

The differential in birth outcome measures between African Americans and Whites in the US widens with increasing African American maternal age [81,82], and has been tentatively attributed to early and continuing deterioration in African American maternal health over the life-course, "weathering," which is mediated by racial discrimination and allostatic load [81–86]. Furthermore, and perhaps counterintuitively, Collins et al. found that women with the highest levels of education, who also report the highest levels of discrimination, have the highest proportion of very LBW births [87]. However, US-born Mexican-Americans, one of the most disadvantaged populations, do not show "weathering," even with long-term residence in low-income neighborhoods [88], and they generally have lower rates of LBW than US Whites [73]. This relative health advantage is attributed to social supports and other nurturing ethno-cultural practices [89,90].

Infants born to first generation migrant mothers have higher birth weights than infants born in the maternal country of origin [91], perhaps, in part, because healthier people have chosen to migrate [92]. However, birth weights in the subsequent "more established" generations are not maintained at that level, which has been attributed to negative effects of environmental factors and adverse experiences with acculturation in the adopted country. Outcomes were generally better in those who live among a concentration of people of the same ethnic group [74,93–95].

8 SOME SUPPORTING OBSERVATIONS

8.1 The special case of Japan

Japan is an exception to the general associations of LBW and CKD with disadvantage. Japan has superb health statistics, with a life expectancy in 2010 of 82.8 years [28] and one of the lowest infant mortality rates in the world (2 per 1000 live births) [33]. However, it has surprisingly high rates of both LBW (10% in 2012) [34,35], and of renal failure, with an incidence of RRT for terminal renal failure of 286 per million [96]. Low glomerular density seen on renal biopsies is compatible with lower nephron endowment [97], and regional distribution of RRT incidence rates correlate approximately with regional distribution of rates of LBW [98,99]. Exacerbations of LBW rates for a period in some regions were tentatively attributed to policies of limiting recommended weight gain during pregnancy to <8 kg, which were intended to facilitate delivery and reduce risks for gestational diabetes, preeclampsia, and hypertension [100].

8.2 Case study of remote-living Australian Aborigines

Falling infant mortality with improved survival to adult life, against a background of LBW, is a major determinant of the changing health profiles of remote-living Aboriginal people in Australia. The trajectory of the Tiwi people of the Top End of the Northern Territory illustrates the paradigm [101–104]. Before the 1950s, most babies were born in the bush and birth weights were not recorded. When first recorded, starting in 1956, birth weights were very low, and infant and childhood mortality were very high, with higher death rates in lower birth weight subjects (Fig. 23.11). Indeed, deaths of the "under 15s" constituted the majority of all deaths. Introduction of more systematic maternal and child health programs produced a precipitous fall in early deaths, across the birth weight spectrum (Fig. 23.12A–B). In less than 30 years, the vast majority of LBW Tiwi babies were surviving to adult life; the population structure was maturing, and the size of the Tiwi population tripled within 50 years. However, the health of those who have survived to adult life fulfill the predictions of the Barker hypothesis (Fig. 23.12C). Rates of albuminuria, levels of blood pressure, cardiovascular events, and hospitalizations for chronic lung disease are all increased in LBW subjects, and rates of natural death are inversely correlated with birth weights [37,104–106]. Natural deaths are increased twofold in LBW adults up to the age of 41 years [102] (Fig. 23.13). The association with LBW in those adults is especially marked for pulmonary deaths, which is compatible with the ranked order of cause of excess deaths in Tiwi infants and children [101]. However, renal deaths are also increased almost twofold (Fig. 23.14). As management of other chronic diseases has improved, competing mortality has fallen and renal disease has more opportunity to pursue its more indolent course to renal failure.

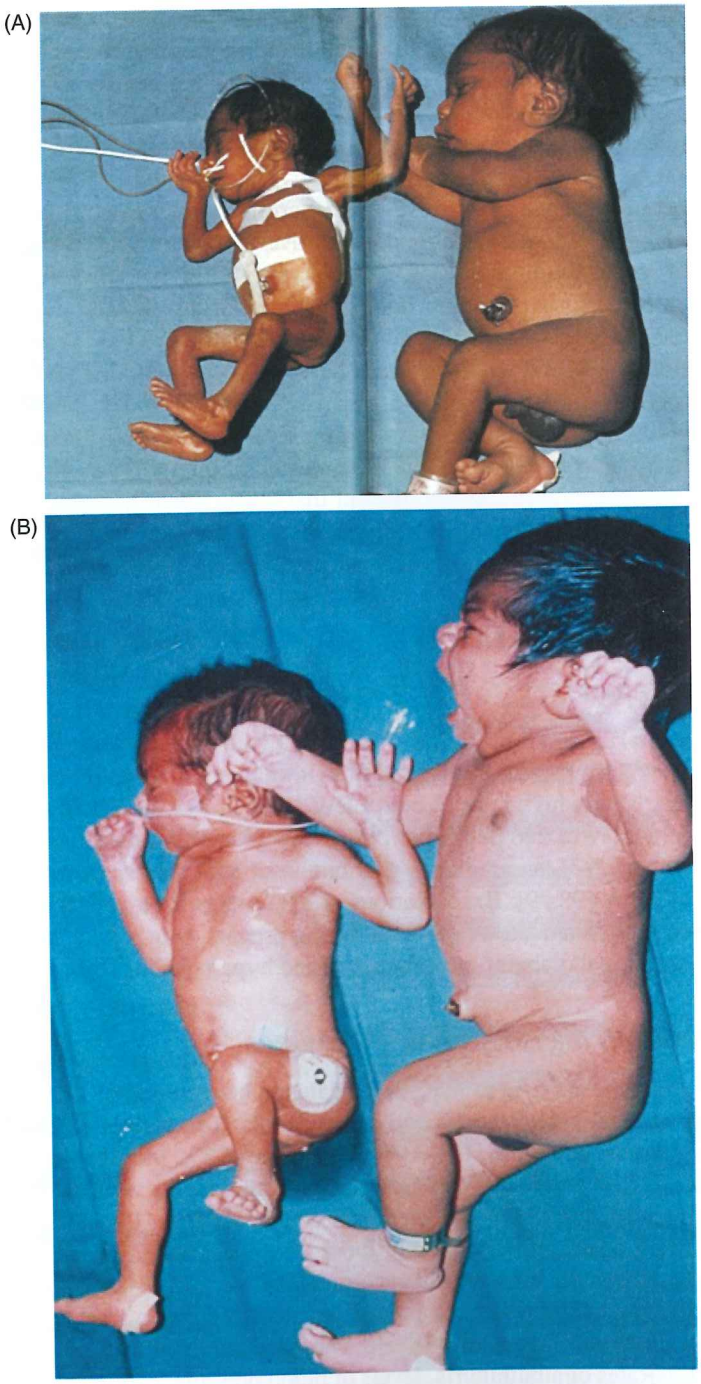
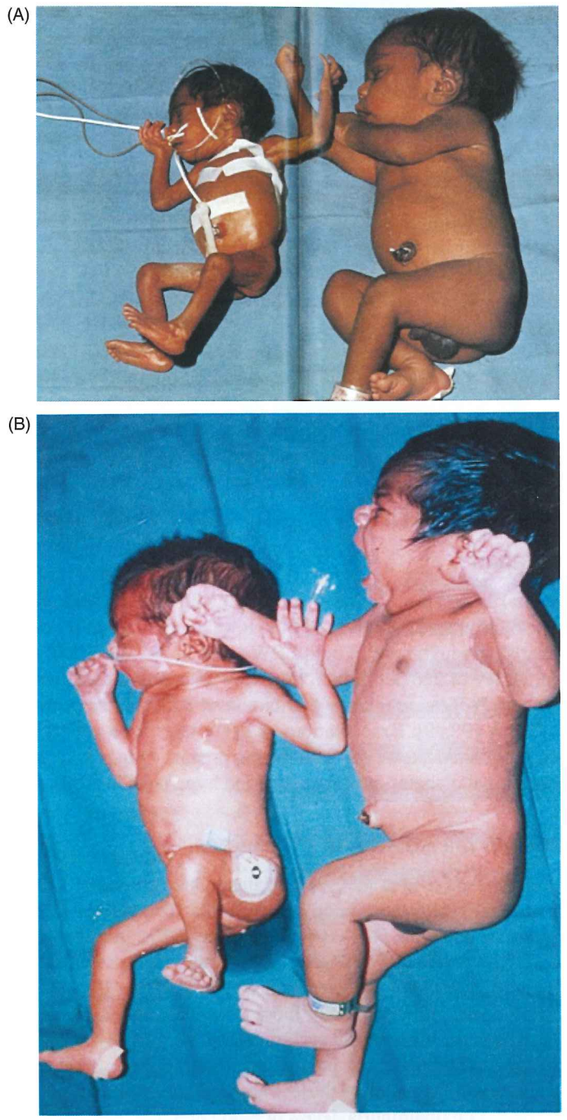


FIGURE 23.11 Newborn remote Aboriginal babies with varying degrees of growth restriction, each compared with more robust newborns. (A) Severely growth restricted. (B) Moderately growth restricted. *(Personal communications, courtesy of Dr Alan Walker and Dr Sue Sayers, Royal Darwin Hospital and Menzies School of Health Research, Darwin, Northern Territory, Australia.)*



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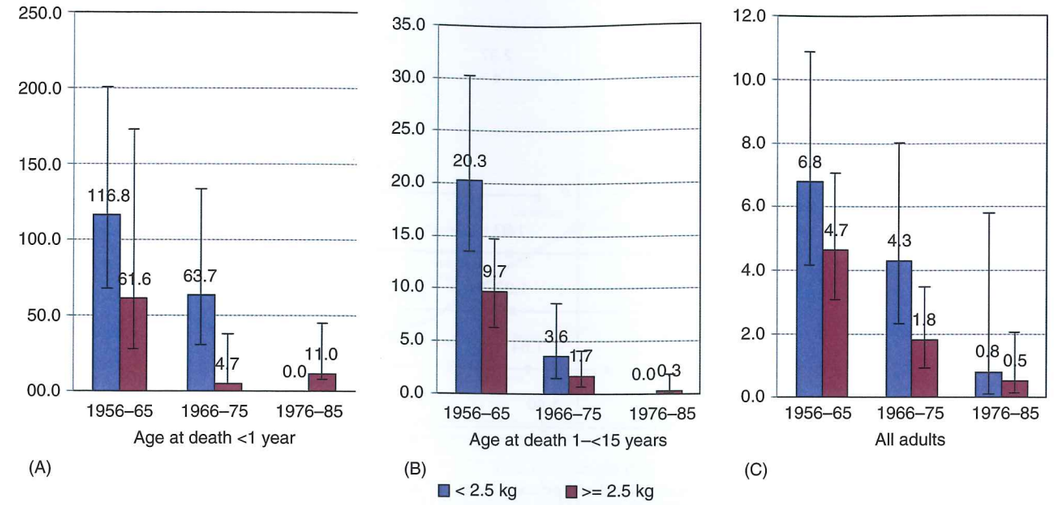


FIGURE 23.12 Rates of natural death in a remote Australian Aboriginal community in infants (n = 35), children (n = 56), and adults (n = 61) by birth interval and birth weight below and above 2.5 kg. (A) Infants (<1 year), (B) children (1–<15 years), (C) adults (≥15 years). Note: Rates are expressed as deaths per 1000-person years, the mean birth weights (kg) of all births by birth interval and percentage <2.5 kg, expressed as mean (SE), % are; 1956–65 = 2.64(0.49), 39.2, 1966–75 = 2.68(0.55), 34.7, 1976–85 = 2.87(0.53), 22.8. *(From Hoy WE, Nicol JL. Birthweight and natural deaths in a remote Australian Aboriginal community. Med J Aust. 2010;192(1):14–9 [101].)*

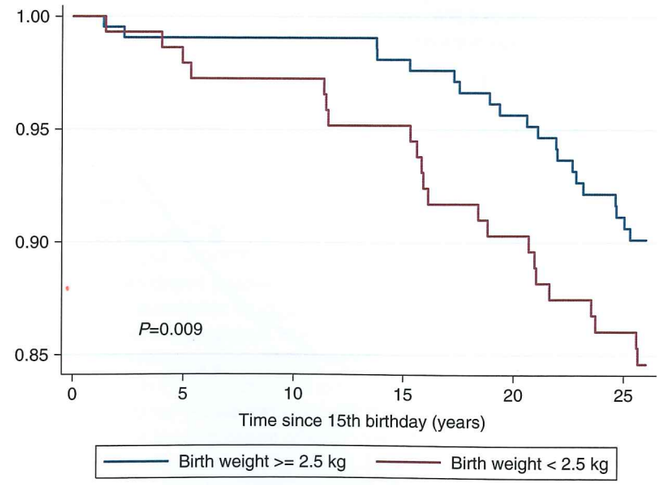


FIGURE 23.13 Kaplan Meier curves for all-cause natural death (n = 42) by birth weight, <2.5 kg versus ≥2.5 kg, in adults (15− < 41 years) (n = 889) from a remote Australian Aboriginal community. Note: Survival adjusted for year of birth and sex.

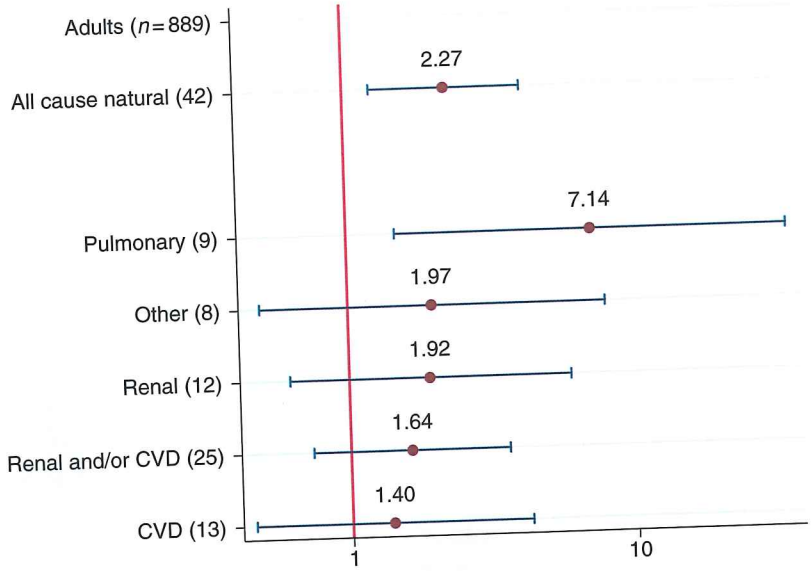


FIGURE 23.14 Hazard ratios (95% CI) for all-cause natural and primary causes of death by birth weight, <2.5 kg versus ≥2.5 kg, in adults (15– < 41 years) (*n* = 889) from a remote Australian Aboriginal community. *Note: Hazard ratios are calculated by the Cox proportional hazard method, adjusted for year of birth and sex.*

8.3 Evaluation of associations

There were insufficient data on screening programs to reliably assess relationships of population-based rates of CKD with LBW. However, while acknowledging the incomplete data from more disadvantaged countries, CKD death rates as recorded in the 2013 Global Burden of Disease Report data appear to be higher in selected countries with a high proportion of LBW [34,107,108]. This is demonstrated in Fig. 23.15 in a selection of countries, or groups within countries, that are relatively homogeneous in ethnicity (≥85% of the population are of a single ethnic classification [109])., Fig. 23.16 shows some correlations between reported rates of LBW and incidence of people starting RRT, in selected settings [96]. Populations were only included if ethnicity was homogeneous [110], where there is relatively unrestricted access to RRT for

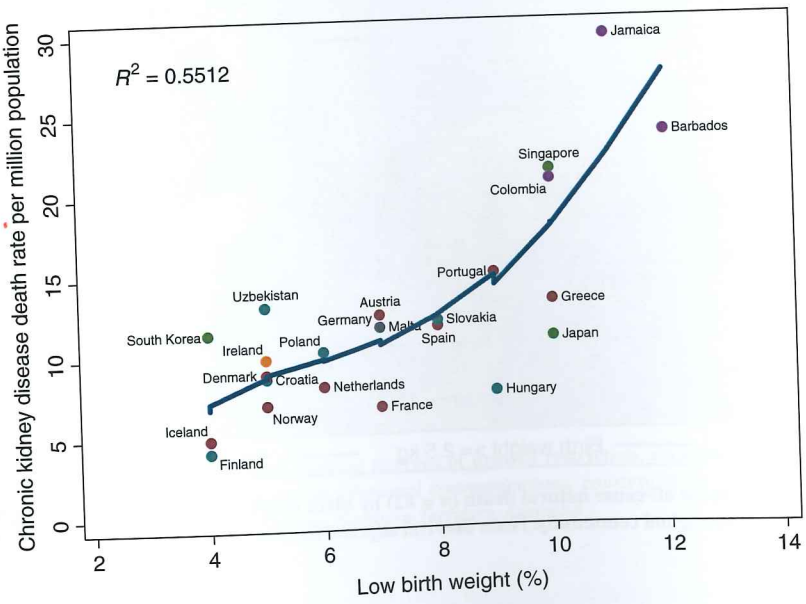


FIGURE 23.15 Chronic kidney disease deaths, 2013 and low birth weight for selected countries. Notes: Deaths were age-standardized to an estimated 2013 standard world population using WHO 2001 methodology and United Nations Population Division data [108]. *(Adapted from UNICEF Global Databases, 2009–2013 reference years, 2014 and IHME Global Burden of Disease Study 2013 [34,107,109].)*

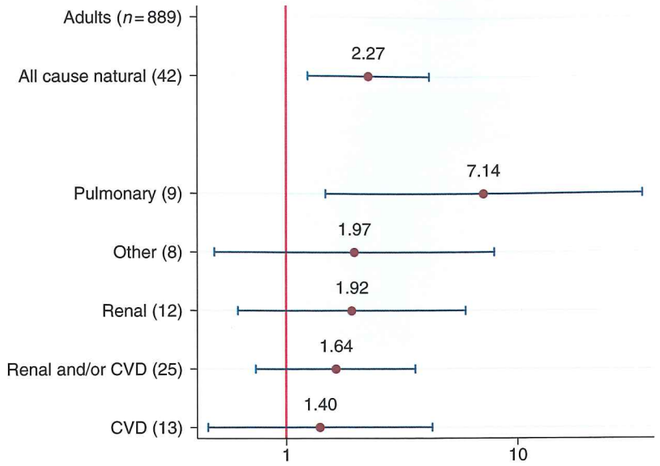
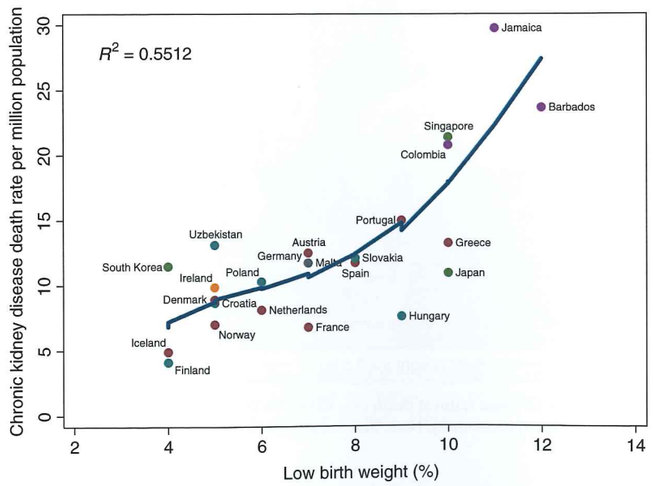


FIGURE 23.14 Hazard ratios (95% CI) for all-cause natural and primary causes of death by birth weight, <2.5 kg versus ≥2.5 kg, in adults (15– < 41 years) (*n* = 889) from a remote Australian Aboriginal community. *Note: Hazard ratios are calculated by the Cox proportional hazard method, adjusted for year of birth and sex.*

8.3 Evaluation of associations

There were insufficient data on screening programs to reliably assess relationships of population-based rates of CKD with LBW. However, while acknowledging the incomplete data from more disadvantaged countries, CKD death rates as recorded in the 2013 Global Burden of Disease Report data appear to be higher in selected countries with a high proportion of LBW [34,107,108]. This is demonstrated in Fig. 23.15 in a selection of countries, or groups within countries, that are relatively homogeneous in ethnicity (≥85% of the population are of a single ethnic classification [109])., Fig. 23.16 shows some correlations between reported rates of LBW and incidence of people starting RRT, in selected settings [96]. Populations were only included if ethnicity was homogeneous [110], where there is relatively unrestricted access to RRT for



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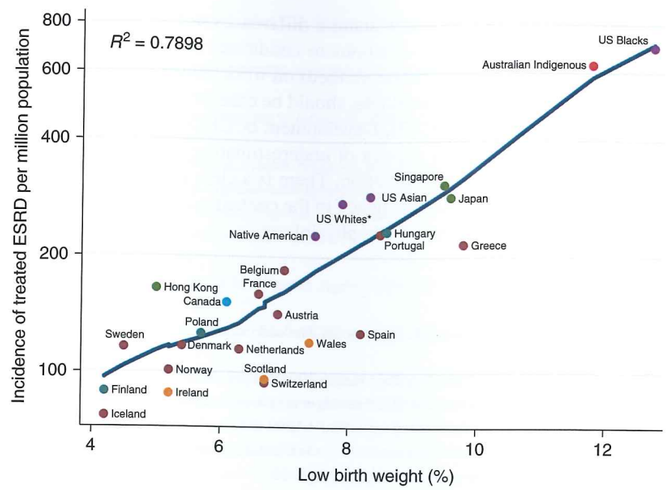

FIGURE 23.16 Relationship between incidence of renal replacement therapy per million of population, 2013 and percent low birth weight worldwide. Note: Low birth weight % reference year range 2009–2013. *(Adapted from UNICEF, 2014 and USRDS, 2015 [34,96,109,110].)*

people with terminal renal failure. Weaknesses in these analyses include use of recent rates of LBW, rather than historical values, and inability to control for other factors, such as obesity, that influence renal failure risk. For RRT, they also include its varied application of that treatment on clinical and other grounds. Nonetheless, there is a strong inverse relationship between RRT incidence rates and recent LBW rates of the referent populations, which applies whether the high incidence outliers (Australian Aborigines and African American) are included or excluded.

9 CONCLUSIONS

There is a strong argument that rates of LBW and preterm birth signal the degree of disadvantage in a population. Disadvantage negatively influences the growth and health of females and males who ultimately become parents, and the resulting fetal growth restriction and premature birth in their offspring impair their health and increase their death rates, risks which are transmitted over several generations. Improving health services continue to extend life beyond childhood and delay death in adults, but the factors that drive LBW and preterm birth are deeply embedded over multiple generations, and their mitigation is a much longer-term challenge.

The WHO review by Kramer [22] states that: "Modifiable factors with large effects on intrauterine growth or gestational duration should be targeted for public health intervention in the two settings, with an emphasis on IUGR in developing countries and prematurity in developed countries. Future research should focus on factors of potential quantitative importance for which data are either unavailable or inconclusive. In developing countries, the most important of these for intrauterine growth are caloric expenditure (maternal work), antenatal care, and certain vitamins and trace elements. For prematurity, especially in developed countries, factors deserving further study include genital tract infection, antenatal care, maternal employment and physical activity, and stress and anxiety."

CKD is only one of several conditions whose expression is facilitated by poor early beginnings. Indeed, the popular interpretation of CKD as a multiplier of the expression of other comorbidities [111] could merely reflect their shared early life risk factors. However, CKD is the only condition for which, in first world environments, a treatment is widely applied to prolong life for persons with end organ failure. The costs of such treatment are out of reach for developing countries, and pose severe budgetary burdens in some countries where RRT is now freely available. Primary prevention and prompt diagnosis and treatment of established disease to reduce its progression are clearly the best investments. These interventions must be incorporated within programs to address chronic diseases more broadly.

The associations of LBW and preterm birth with CKD have many implications. In a plausible example, DeFreitas et al. [46] predict that a person with nephropenia from the neonatal period, manifest as impaired kidney function by the age of 2, might develop renal failure by age 40 years, losing 30–40 years of life expectancy. The speculation by Barker and Lackland

[112] that different birth weight profiles could drive substantial differences in CKD rates among populations has proven prophetic. Investigation of the relevance of such associations to conditions such as CKDu seems wise, and could more broadly influence public health interventions than a selective focus on work related factors or the environment [11,12]. Taal and Brenners recommend that birth weight, where available, should be considered in evaluation of every CKD patient and, additionally, in all potential living kidney donors [113]. Development of CKD in living Aboriginal related kidney donors within a few years of donation [114] demonstrates the risk of underestimating modest degrees of nephron deficiency, and the inadequacy of current techniques to define that condition. There is a clear imperative to develop noninvasive imaging techniques to define nephron number, and assess its adequacy in the context of age and current size, for clinical and epidemiological purposes, and to better understand kidney pathophysiology.

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