Beyond Newborn Survival Paper 2

Preterm birth–associated neurodevelopmental impairment estimates at regional and global levels for 2010

Hannah Blencowe1, Anne CC Lee2,3, Simon Cousens1, Adil Bahalim4, Rajesh Narwal1,5, Nanbert Zhong6,7, Doris Chou8, Lale Say9, Neena Modi9, Joanne Katz2, Theo Vos10,11, Neil Marlow12 and Joy E. Lawn13,14

BACKGROUND: In 2010, there were an estimated 15 million preterm births worldwide (<37 wk gestation). Survivors are at risk of adverse outcomes, and burden estimation at global and regional levels is critical for priority setting.

METHODS: Systematic reviews and meta-analyses were undertaken to estimate the risk of long-term neurodevelopmental impairment for surviving preterm babies according to the level of care. A compartmental model was used to estimate the number of impaired postneonatal survivors following preterm birth in 2010. A separate model (DisMod-MR) was used to estimate years lived with disability (YLDs) for the global burden of disease 2010 study. Disability adjusted life years (DALYs) were calculated as the sum of YLDs and years of life lost (YLLs).

RESULTS: In 2010, there were an estimated 13 million preterm births who survived beyond the first month. Of these, 345,000 (2.7%, uncertainty range: 269,000–420,000) were estimated to have moderate or severe neurodevelopmental impairment, and a further 567,000 (4.4%, (445,000–732,000)) were estimated to have mild neurodevelopmental impairment. Many more have specific learning or behavioral impairments or reduced physical or mental health. Fewest data are available where the burden is heaviest. Preterm birth was responsible for 77 million DALYs, 3.1% of the global total, of which only 3 million were YLDs.

CONCLUSION: Most preterm births (>90%) survive without neurodevelopmental impairment. Developing effective means of prevention of preterm birth should be a longer term priority, but major burden reduction could be made immediately with improved coverage and quality of care. Improved newborn care would reduce mortality, especially in low-income countries and is likely to reduce impairment in survivors, particularly in middle-income settings.
births affected, survival by gestational age, and risk of disability have not been published since the 1996 GBD version (12). The Expert team for preterm birth involved in GBD2010 overlaps with the author group on this paper, and we discuss the parameter inputs and regional and global estimates of specific outcomes associated with preterm birth in GBD2010. In addition, since the inputs were finalized for GBD2010, further data have been published, and additional data sets became available for analyses, for example, to improve the coverage of care assumptions used throughout this supplement. This is in the spirit of continually improving the input data. Where the inputs or methods differ from GBD, this will be noted (13).

METHODS
Definitions
The World Health Organization (WHO) defines preterm birth as any birth before 37 completed weeks of gestation (fewer than 259 days from the first day of the women's last menstrual period (14)). This is commonly subdivided based on gestational age: extremely preterm (<28 wk), very preterm (28–31 wk), and moderate and late preterm (32–36 wk), since decreasing gestational age is associated with increasing mortality, disability, and a greater requirement for intensive neonatal care if survival is to be assured, with higher associated costs.

Estimating the burden of preterm birth is challenging due to the paucity of gestational age–specific data. Given the relatively recent recognition of the importance of gestational age rather than birth weight in determining outcome, most studies have presented data by birth weight alone. Widespread early ultrasound screening has improved gestational age assessment in most high-income and many middle-income countries. However, this requires skilled technicians equipment and is most accurate when undertaken in the first trimester, limiting its use in many low- and middle-income settings. Without early ultrasound screening, gestational age assessment uses less-accurate methods based on last menstrual period or newborn physical characteristics (15). When gestational age data were not available, we used commonly applied birth weight proxies, namely, <1,000 g for extremely preterm birth (<28 wk) and 1,000 to <1,500 g for very preterm birth (28–31 wk) (Supplementary Information online).

We estimated long-term (present at 2–5 y of age) mild and moderate/severe neurodevelopmental impairment among postneonatal survivors of preterm birth. See Table 1 and the methods paper of this supplement for full definitions (13).

Data Searches and Meta-Analyses
A systematic literature review was undertaken of the main online literature databases including Pubmed/Medline, Embase, CAB abstracts, Popline, Web of Science, Cumulative Index to Nursing and Allied Health (CINAHL) Latin American and Caribbean Health Science (LILACS), and WHO Regional library databases, applying the general search strategy described in the methods paper of this supplement (13). Search terms used included multiple variants of terms covering the following areas “preterm/premature” and “birth/labor” or “newborn/infant,” “mortality/death,” and “outcome/impairment” and used Medical Subject Headings terms when available (see Supplementary Information online for full details of search terms, dates, and inclusion criteria). Snowball searching was used to identify additional studies by screening the reference lists of retrieved studies. Data were abstracted if the study fulfilled the inclusion criteria, regardless of the year of birth of the cohort. However, in view of the rapid changes and progress in neonatal intensive care in low mortality settings over the past decades, especially for the preterm baby, only studies with birth cohorts with a median year of 2000 or later were included in the main analysis. Data on the outcome of preterm-born neonates with congenital abnormalities were excluded.

Standard meta-analysis techniques were used to obtain summary estimates of the parameters of interest including neonatal CFR, gender, and risk of impairment by gestational age and access to care (Figure 2). Heterogeneity across studies was assessed using I² and the χ² test. Where evidence of heterogeneity was present (I² > 70% or P < 0.05), a random-effects meta-analysis model was used.

Overview of Modeling Approach
A three-step compartmental model was constructed, using the estimated input parameters to estimate neurodevelopmental impairment among postneonatal survivors of preterm birth (Figure 2) (13). This approach differs from GBD2010 in that the focus is on 2010 without estimating time trends for the condition or for sequelae. The methods applied in GBD are summarized in the methods paper of this supplement and detailed elsewhere (13,16). In step 1, we estimated the prevalence of preterm birth among live births, by sex, as this is a determinant of mortality and morbidity outcomes. In step 2, we estimated the number of postneonatal survivors, and in step 3, the number of these survivors who were impaired (Figure 2). The steps of the compartmental model were applied in sequence for the live births in each country with more than 10,000 births for the year...
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2010 (17). Unpublished data for the same live birth series was used to estimate the number of live births by sex. All results are presented at the regional level using the GBD super-regional grouping (13). We quantified the uncertainty surrounding these estimates by taking 1,000 random draws of the input parameters at each step, assuming a normal distribution with mean equal to the point estimate of the parameter and SD equal to the estimated standard error of the parameter. We summed the data at worldwide or regional level for each draw and present the 2.5th and 97.5th percentiles of the resulting distributions as the uncertainty range.

### RESULTS

A total of 14,929 titles and abstracts were reviewed, and 862 studies contributed to the estimation of one or more parameters. A summary of all the parameter values used is given in Table 2 (see also Supplementary Information online). A summary of the regional results is given in Table 3.

**Step 1: Preterm Live Birth Prevalence**

**Preterm live birth prevalence.** National preterm birth rates for 2010 were estimated using two regional multilevel statistical models including data from national registries or statistical offices, Reproductive Health Surveys, unpublished data, and published papers identified through a systematic review. These included 738 reported data inputs from 99 countries, with the majority (547/738) of the data...
inputs coming from high-income countries. Full details of the searches, methodology input data, statistical modeling, and results have been published elsewhere, including the estimates for 2010 for 184 countries and time trends for 65 countries (1).

Gestational age subdivisions. The distribution of preterm births by gestational age subgroup was estimated from a meta-analysis of 345 data points (131 million live births) (1). Based on these studies, we estimate that 5.2% (95% CI: 5.1–5.3%) of all preterm births were at less than 28 wk; 10.4% (95% CI: 10.3–10.5%) at 28–31 wk and 84.3% at 32–36 wk (95% CI: 84.1–84.5%). Eighty-five percent of those born at 32 wk or more were born between 34–36 wk.

Sex differences in preterm live-birth prevalence. Data from 13 studies from the United States/Europe suggest that 54.6% (95% CI: 53.9–55.4%) of preterm births are in males and that risk ratio for preterm birth among males compared with females is 1.14 (95% CI: 1.11–1.17) (Table 2; Supplementary Information online) No data fulfilling the inclusion criteria were available from middle- or low-income settings, and therefore, the male to female risk ratio for preterm birth was assumed to be constant across all countries in all regions. The sex-specific prevalence of preterm birth was estimated by first calculating the absolute risk of preterm birth in males and females and applying this to the sex-specific live-birth data by country (see Supplementary Information online).

Prevalence estimates. We estimate that of the 14.9 million preterm births (uncertainty range: 12.3–18.1 million) in 2010, 8.2 million (54.9%, 7.4–9.5 million) were males (Figure 3). An estimated 0.8 million (0.8–0.9 million) were <28 wk, 1.6 million (1.5–1.7 million) were 28–31 wk, and 12.6 million (12.3–14.0 million) were 32–36 wk.

Step 2: Calculation of the Number of Postneonatal Survivors

Effect of sex on case fatality rate. While evidence supports lower survival for male neonates at all gestations when compared with females, insufficient data were available to include sex-specific mortality risks in the model (18–20).

Coverage and quality of care. We used the country neonatal mortality rate (NMR) as a proxy for access to and quality of newborn care and classified countries into three categories (Table 2) (13). We considered three care scenarios:

1. Full availability of all levels of neonatal care (including neonatal intensive care unit (NICU));
2. Some availability of specialized neonatal care (including neonatal special care), and
3. No access to NICU or neonatal special care, since outcomes after preterm birth are highly dependent on both gestational age and the quality of care received.

See the methods paper of this supplement (13) and Supplementary Information online for further details.
### Table 2. Countries (184) according to level of neonatal mortality, showing a summary of input data to the compartmental model for preterm around the year 2010

| Countries according to level of NMR | Level 1 | Level 2 | Levels 3/4/5 |
|------------------------------------|---------|---------|--------------|
| No. of countries in 2010           | 46      | 62      | 76           |
| No. of live births in 2010          | 13,261,000 | 40,271,000 | 81,148,000 |
| **Step 1** Preterm birth prevalence data (per 100 live births) | 30 countries | 28 countries | 41 countries |
| N = 11.0 million                    | 415 datasets | 187 datasets | 136 datasets |
| Data range: 4.1–16.4%              | Medians: 6.8% | 5.9% | 8.5% |
| Gestational age subdivisions        | 345 data points; <28 weeks: 5.2% (95% CI: 5.1–5.3%); 28–31 weeks: 10.4% (95% CI: 10.3–10.5%); and 32–36 weeks: 84.3% (95% CI: 84.1–84.5%) |
| Relative risk of preterm birth for males compared to females | 10 countries; 13 datasets; N (live births) = 8.6 million; pooled estimate: 1.14; and (95% CI: 1.11–1.17) |
| **Step 2** Gestation-specific preterm birth case fatality risk (per 100 live births in gestational age group) | 21 countries | 38 countries |
| N (preterm births) = 388,253       | 36 datasets | 40 datasets |
| Whole population                   | 28.3% (95% CI: 25.4–31.2%) | 99% (95% CI: 98–100%) | 86.4% (95% CI: 78.9–93.9%) |
| Limited basic care                 | 5.8% (95% CI: 5.1–6.5%) | 61.4% (95% CI: 55.5–67.3%) | 41.3% (95% CI: 36.8–45.9%) |
| Neonatal special care              | 9% (95% CI: 89–90%) | 9% (95% CI: 85–87%) | 9% (95% CI: 82–84%) |
| NICU                               | 1.8% (95% CI: 1.5–2.3%) | Assumed to be the country NMR * 2.05 (95% CI: 1.55–2.70) |
| 32–36 wk                           | 0.7% (95% CI: 0.6–0.8%) | | |
| **Step 3** Risk of moderate/severe long-term neurodevelopmental impairment after preterm birth (per 100 preterm survivors in gestational age group) | 17 countries, 20 datasets, N (survivors) = 9,369 | 7 countries, 7 datasets, and N (survivors) = 498 |
| N (preterm births) = 19,191         | 24.5% (95% CI: 20.2–28.8%) | All <32 wk: 24.6% (95% CI: 15.3–33.9%) |
| <28 wk, 28–31 wk, and 32–36 wk     | 12.2% (95% CI: 6.1–18.2%) | No data. Assume 1.8% as per low mortality settings |
| 9 countries, 23 datasets, and N (survivors) = 19,191 | 1.8% (95% CI: 1.5–2.3%) | | |
| Risk of mild long-term neurodevelopmental impairment after preterm birth (per 100 preterm survivors in gestational age group) | 3 countries | 4 countries |
| N (preterm births) = 237            | 33.9% (95% CI: 28.6–39.3%) | All <32 wk: 32.4% (95% CI: 15.4–49.4%) |
| <28 wk, 28–31 wk, and 32–36 wk     | 16.5% (95% CI: 13.6–19.3%) | No data. Assume 3.4% as per low mortality settings |
| 3.4% (95% CI: 2.5–4.4%) | | |

CI, confidence interval; NICU, neonatal intensive care unit; NMR, neonatal mortality rate.

*aAssuming 85% of those 32–36 wk are 34–36 wk (see gestational age subdivisions) and 32–33 wk = 8.2% (95% CI: 6.5–10.1%) and 34–36 wk = 0.7% (95% CI: 0.6–0.9%). 32–33 wk = 15.9% (95% CI: 11.1–20.7%) and 34–36 wk = 1.2% (95% CI: 1.0–1.5%).
**Gestation-specific case fatality rate by NMR group, gestational age category and level of care available.** These are summarized in Table 2.

### Low-mortality countries (NMR < 5): population-based approach for all gestational ages

For low mortality countries, gestational age–specific neonatal mortality data were abstracted from cohort studies identified from searches, predominantly from NICU, assuming all live-born neonates under 32 wk in these countries have access to NICU. Further searches of statistical databases, including EURO-PERISTAT (21) were used to provide population-based data from countries with more advanced statistical reporting systems and for those born at 32–36 wk. Case fatality risk (CFR) was estimated as 28.3% (95% CI: 25.4–31.2%) for those born at <28 wk; 5.8% (95% CI: 5.1–6.5%) for those born at 28–31 wk; and 0.7% (95% CI: 0.6–0.8%) of those born at 32–36.

### Higher mortality countries (NMR ≥ 5): population-based approach for those born at 32–36 wk

For higher mortality countries, population-based data on neonatal survival of those born preterm are limited. Data from principle investigators collaborating with the Child Health Epidemiology Research Group SGA-Preterm Working Group provided mortality data from 19 low- and middle-income country birth cohorts by gestational age bands: <32 and 32–36 wk (22). Neonatal CFR for neonates born at 32–36 wk is less dependent on availability of intensive care and is mainly affected by basic hygiene, thermal care, extra support for breast feeding, and prompt recognition and treatment of infections. Hence, the survival of this group is closely related to the population NMR and showed a consistent relationship across these 19 studies with a pooled neonatal mortality risk ratio of 2.05 (95% CI: 1.55–2.70) for neonates born at <28 wk; 857,000 (821,000–976,000) born at 28–31 wk; and 645,000 babies (585,000–757,000) born at 32–36 wk.

### Higher mortality countries (NMR ≥ 5): approach based on level of care available for those born at <32 wk

Survival at <32 wk is highly dependent on the care available. In many high-mortality settings, most of these births will be at home, without gestational age assessment, access to specialist hospital care, or birth registration. Population-based data for these babies are problematic, with many community-based studies reporting implausibly high neonatal survival rates among very preterm neonates with limited availability of care, likely due to missed early neonatal deaths (22,23).

For neonates with basic/limited care only, survival for those born at <28 wk is uncommon. We assumed that 99% of all neonates born at <28 wk with no access to neonatal special care would die. For babies born at 28–31 wk, we estimate 61.4% (95% CI: 55.5–67.3) neonatal mortality based on one multisite trial including 96 rural sites in 7 countries (24). We note that this is an underestimate since neonatal deaths occurring after the first 7 d were not captured in this study.

For babies with access to special care only without intensive care, the estimated neonatal mortality was 86.4% (95% CI: 78.9–91.9%; 3 studies) for those born at <28 wk and 41.3% (95% CI: 36.8–45.9%; four studies) for those born at 28–31 wk. With access to NICU care, no strong evidence of a difference in mortality for neonates born at <28 wk was found between NMR 5 to <15 and NMR ≥15 countries, and the pooled estimate of 51.7% (95% CI: 43.3–60.0%; 17 studies) was used for all neonates with access to NICU in countries with NMR ≥5. For neonates born at 28–31 wk with access to NICU care, the pooled estimate of mortality was 15.3% (95% CI: 9.9–20.6%; 10 studies) in NMR 5 to <15 countries and 28.8% (95% CI: 25.2–32.5%; 5 studies) in NMR ≥15 countries.

**Supplementary Information**

Estimates of the number of postneonatal survivors. An estimated 4.3 million preterm neonates had access to NICU care if required (28% of all preterm live births), 2.5 million (17%) to special care only, and 8.2 million (55%) to basic/limited care only.

A total of 2.0 million (uncertainty range: 1.9–2.2 million) of those born preterm are estimated to have died during the first month of life comprising 642,000 babies (613,000–717,000) born at <28 wk; 702,000 babies (653,000–810,000) born at 28–31 wk; and 645,000 babies (585,000–757,000) born at 32–36 wk. This leaves an estimated 13 million (12.7–14.3 million) postneonatal preterm survivors. A total of 51.7% (95% CI: 43.3–60.0%; 17 studies) was used for those born at <28 wk; 702,000 babies (653,000–810,000) born at 28–31 wk; and 645,000 babies (585,000–757,000) born at 32–36 wk. This leaves an estimated 13 million (12.7–14.3 million) postneonatal preterm survivors. 140,000 (130,000–170,000) born at <28 wk; 857,000 (821,000–976,000) born at 28–31 wk; and 12.0 million (11.6–13.2 million) born at 32–36 wk.

### Step 3: Calculation of the Number of Impaired Survivors

#### Sex-specific impairment risk

Although evidence supports increased neonatal morbidity and long-term neurodevelopmental impairment for males at all gestations when compared with females, insufficient data were available to include sex-specific risks in the model (19,25).

#### Gestation-specific impairment risk by NMR group, gestational age category, and level of care

Twenty-six studies reporting neurodevelopmental outcomes were included from the searches described above. Data were pooled in meta-analyses by NMR group. (Table 2 and Figures 4–6; Supplementary Information online) The median age at assessment was 28 mo. The proportion of surviving neonates who developed neurodevelopmental impairment did not vary in a consistent way across studies with differing lengths of follow-up. Where follow-up studies reported neurodevelopmental impairment in survivors who were assessed at several different time points, the data from the assessment nearest to 5 y of age were used, to provide a balance between increasing loss to follow-up in cohorts over time, and concordance of the developmental assessment with later neurodevelopmental and school outcome (26). This may underestimate the risk and severity of impairment for all postneonatal survivors, since the most severely impaired survivors have increased risk of death in childhood and hence may be underrepresented in the follow-up studies used to estimate the risk of impairment. Exclusion of studies with >30% loss to follow-up did not affect the overall result, and hence, no study was excluded on this basis to minimize data loss.
Table 3. Estimated number of preterm births, deaths, and impaired survivors by region in 2010 with YLDs and total DALYs from preterm birth at all ages GBD 2010

| Region                        | Number of live births | Number of preterm births (uncertainty range) | % of worldwide total | Number of neonatal deaths in babies born at <37 wk (uncertainty range) | % of worldwide total | Number of survivors with severe impairment (uncertainty range) | % of worldwide total | GBD 2010 Estimated YLDs due to prematurity in thousands (uncertainty range) | % of worldwide total | GBD 2010 Estimated DALYs due to preterm birth in thousands (uncertainty range) | % of worldwide total | Percentage of DALYs that are from YLDs |
|-------------------------------|-----------------------|---------------------------------------------|----------------------|-------------------------------------------------------------------------|----------------------|------------------------------------------------------------------|----------------------|---------------------------------------------------------------------------|----------------------|-----------------------------------------------------------------------------|----------------------|---------------------------------------------------------------|
| High income                  | 11.7 million          | 1,064,000 (1,047,000–1,124,000)             | 9%                   | 30,200 (28,700–32,700)                                                 | 1%                   | 39,600 (31,600–472,000)                                         | 12%                  | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 12%                  | 2,200 (1,900–2,600) (1,800) (3,400–4,600) (9,300) (3,900) (29,000–45,000) | 3%                   | 16.2%                                                        |
| Eastern Europe/              | 5.4 million           | 413,000 (333,000–517,000)                   | 4%                   | 27,900 (27,300–34,600)                                                 | 1%                   | 16,600 (13,000–21,700)                                          | 5%                   | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 5%                   | 1,500 (1,200–2,000) (1,800) (3,400–4,600) (9,300) (3,900) (29,000–45,000) | 2%                   | 9.5%                                                          |
| Central Asia                 |                       |                                             |                      |                                                                          |                      |                                                                  |                      |                                                                          |                      |                                                                             |                      |                                               |
| Latin America and Caribbean  | 9.9 million           | 851,000 (680,000–1,222,000)                 | 7%                   | 70,300 (69,900–254,900)                                                | 4%                   | 24,400 (20,000–38,000)                                          | 7%                   | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 7%                   | 3,900 (2,057,000–6,650,000) (2,057,000–6,650,000) (2,057,000–6,650,000) | 10%                 | 5.3%                                                        |
| East–Southeast               |                       |                                             |                      |                                                                          |                      |                                                                  |                      |                                                                          |                      |                                                                             |                      |                                               |
| Asia and Pacific             |                       |                                             |                      |                                                                          |                      |                                                                  |                      |                                                                          |                      |                                                                             |                      |                                               |
| North Africa and Middle      | 29.0 million          | 2,808,000 (2,057,000–3,560,000)             | 22%                  | 272,800 (254,900–313,500)                                              | 14%                  | 96,500 (94,000–120,000)                                         | 25%                  | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 25%                  | 151,500 (97,400–168,900) (104,500–165,000) (104,500–165,000) (104,500–165,000) | 19%                 | 10.4%                                                       |
| East Asia and Pacific        |                       |                                             |                      |                                                                          |                      |                                                                  |                      |                                                                          |                      |                                                                             |                      |                                               |
| South Asia                   | 37.1 million          | 911,000 (665,000–1,214,000)                 | 7%                   | 96,500 (94,000–120,000)                                                | 5%                   | 25,100 (19,600–32,000)                                         | 7%                   | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 7%                   | 86,500 (669,000–914,500) (717,300–914,500) (717,300–914,500) (717,300–914,500) | 29%                 | 4.0%                                                        |
| Sub-Saharan Africa           | 32.1 million          | 4,954,000 (3,724,000–6,256,000)             | 28%                  | 818,900 (717,300–914,500)                                              | 34%                  | 669,600 (669,000–781,600)                                       | 48%                  | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 48%                  | 669,600 (1,942,000–2,191,000) (1,942,000–2,191,000) (1,942,000–2,191,000) | 48%                 | 2.3%                                                        |
| Total                        | 135 million           | 14,900,000 (12,300,000–18,200,000)          | 100%                 | 1,985,600 (1,942,000–2,191,000)                                        | 100%                 | 781,600 (669,000–880,000)                                       | 100%                 | (270–500) (100–190) (160–290) (600–1,080) (130–230) (610–1,150) (280–470) | 100%                 | 566,700 (444,600–731,900) (444,600–731,900) (444,600–731,900) | 100%                | 1.9%                                                        |

DALYs, disability adjusted life years; GBD, global burden of disease; YLD, years lived with disability.

*Including 347 (212–508) from isolated visual impairment from retinopathy of prematurity.

Figure 3. Number of preterm births in 2010 for world region according to the sex of the baby. Males are shown in dark gray, females in light gray.
Data on long-term risk of neurodevelopmental impairment after very preterm birth (<32 wk) are only available for survivors in high-mortality settings who have benefited from NICU care. The risk of neurodevelopmental impairment in the few very preterm neonates who survive the neonatal period without access to NICU care is likely to be lower, given the substantial mortality risk in this group and those who survive are a relatively more mature population with less immediate morbidity. We assumed, as a conservative estimate, the risk of impairment postneonatal survivors born at <32 wk without access to NICU care to be as a minimum the same as the risk for those born at 32–36 wk in high-income settings (Table 2).

Increasing evidence suggests a small but significant risk of neurodevelopmental impairment after late preterm birth, even in the absence of acute neonatal complications. No population-based data on the risk of long-term impairment after moderate-to-late preterm birth was available from high-mortality settings. Hence, we assumed that the impairment rate for those surviving moderate-to-late preterm birth to be similar to that from population-based data for postneonatal survivors born at 32–36 wk in high-income settings (Table 2).

**Estimates of the number of impaired survivors.** We estimate that at least 911,000 (uncertainty range: 775,000–1,102,000) of postneonatal preterm survivors (7%) suffer long-term neurodevelopmental impairment. This comprises 345,000 (uncertainty range: 269,000–420,000) who are moderately or severely affected and a further 567,400 (445,000–732,000) with mild neurodevelopmental impairment. Worldwide, 52% of those born at <28 wk, 24% of those born at 28–31 wk, and 5% of those born at 32–36 wk and surviving the neonatal period are estimated to have some degree of neurodevelopmental impairment (Figure 7).

**GBD2010-Specific Inputs, Methods, and Results**

GBD2010 used an approach similar to the three steps defined above to estimate the number of impaired survivors after preterm birth but for 1990–2010 (as opposed to 2010 only).

**Key differences between the three steps between GBD2010 and the compartmental model.** With respect to data inputs, the final date of the searches for the inputs to GBD2010 was June 2011 and hence did not include additional data published after this date which was available for the compartmental model presented here only. GBD2010 used risk of impairment data from 34–36 wk group to apply to the entire 32–36 wk group. Regarding GBD methods, a single pooled estimate of CFR and risk of impairment by gestational age category was used for all neonates in a given NMR group and did not take access to neonatal care into account. Hence, the estimated number of preterm births by region in GBD2010 was slightly lower but within the uncertainty range when compared with the method described in this paper. The estimated number of impaired survivors was lower in all regions in the GBD2010 model. The higher estimates in the compartmental model are primarily driven by the revised CFR by level of care assumptions which
estimates fewer deaths at all gestational ages in the highest burden regions and the increased impairment risk from using new gestation-specific data for those born at 32 and 33 wk in all regions (Supplementary Information online). If these revisions were taken into account in GBD, the estimated number of years lived with disability (YLDs) may be substantially higher.


**Figure 6.** Meta-analysis of studies reporting moderate/severe impairment outcomes for babies born at less than 32 wk in countries with neonatal mortality rate (NMR) ≥5 in 2000–2010.

| Study ID | ES (95% CI) |
|----------|-------------|
| Al-Marzooq | 0.15 (0.07, 0.23) |
| Khan | 0.24 (0.15, 0.33) |
| Reis | 0.45 (0.36, 0.54) |
| Were | 0.12 (0.06, 0.17) |
| Ballota | 0.38 (0.29, 0.47) |
| Nouailia | 0.18 (0.05, 0.22) |
| Gocer | 0.27 (0.19, 0.35) |
| Overall | 0.25 (0.15, 0.34) |

*Note: Weights are from random effects analysis.*

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**Figure 7.** Worldwide deaths and disability for babies born preterm in 2010.

Estimates shown are all from the 3 step compartmental model outlined in this article. Note that the mortality estimates here refer to all deaths in preterm babies, not preterm specific complications as a direct cause of death, which the United Nations estimates at one million deaths and GBD2010 suggests 900,000. Furthermore, a compartmental model and case fatality risk (CFR) are more uncertain for cause of death estimation. Given these considerations the estimates are consistent with an estimate of preterm birth as risk factor for neonatal mortality, but a full comparative risk analysis is the next step. GBD, global burden of disease.
GBD2010 included three further steps beyond the compartmental model described above:

1. A Bayesian meta-regression method developed for the GBD, DisMod-MR, was used to estimate the prevalence of long-term impairments in 2010 by age, sex, and country including additional data regarding excess mortality risk in impaired survivors (15).

2. The number of YLDs at all ages were calculated as the prevalence of impaired survivors at all ages multiplied by the disability weight scores derived for the GBD2010 study (13,34). In DisMod-MR, all preterm births with moderate-to-severe outcomes were modeled together. A Swedish register of 90 children with cerebral palsy due to preterm birth was used to apportion the distribution of severity to motor impairment, cognitive impairment, seizure disorder, blindness, and possible combinations (35). The final disability weight used for moderate-to-severe neurodevelopmental impairment for high-income regions was 0.38 (uncertainty range: 0.29–0.49) and 0.42 (uncertainty range: 0.32–0.53) in low- and middle-income regions. The higher disability weights in low- and middle-income regions are because the epilepsy disability weights distinguish those with and without treatment differently. Separate calculations were made for ROP, but disability for vision loss was only awarded to an estimated proportion of isolated cases of ROP without any other impairments as blindness in those with other impairments was taken into account in a combined disability weight for all moderate to severely impaired cases. Mild outcomes were modeled separately assuming that 50% of those with mild impairment had isolated mild motor problems, and 50% had mild motor and mild cognitive impairment. The final disability weight used for mild neurodevelopmental impairment was 0.03 (uncertainty range: 0.02–0.05).

3. The number of disability adjusted life years (DALYs) were then calculated as the sum of years of life lost (YLLs) due to premature mortality from preterm birth and YLDs (11,13). YLLs for preterm birth in 2010 were calculated for GBD2010 using the Cause of Death Ensemble model (CODEm) and standard life expectancy tables (13,36). This includes deaths at all ages due to direct complications of preterm birth only and is based on 3,363 vital registration, 225 verbal autopsy, and 25 surveillance data sources.

**Discussion**

Of 15 million (12.3–18.2 million) preterm births in 2010, 13.0 million (12.7–14.3 million) were estimated to survive the neonatal period. An estimated 0.9 million (uncertainty range: 0.8–1.1 million) of these postneonatal survivors will suffer long-term neurodevelopmental impairment with 345,000 (uncertainty range 269,000–420,000) moderately or severely affected. There is a well-recognized gradient of increasing risk of mortality and adverse developmental outcomes with decreasing gestational age at birth from early term (37–38 wk) through to the most premature survivors (32,37–42). Preterm brain injury results from developmental vulnerability given that the brain weighs only 65% of its full-term weight at 34 wk and glial cell migration continues to 36 wk (43) and compounded by brain injury associated with neonatal complications such as respiratory distress/hypoxemia, infection, hyperbilirubinemia, and hypoglycemia (44–47). Those born preterm are at higher risk of having complex medical, psychological, educational, and socioeconomic needs, placing a burden on both families and communities even in high-income settings (48–50). Few reports have quantified the long-term excess postneonatal mortality among impaired survivors in low- and middle-income settings; however, this is likely to be high given seizures, aspiration pneumonia, feeding difficulties, and potentially by reduced care-seeking practices.

Our CFR-based estimates suggests that ~2.0 million preterm neonates born in 2010 died during the first month of life both from direct complications of preterm birth (most deaths in those born at <32 wk) and from other causes where preterm birth was a risk factor (Figure 8). Caution should be applied in interpreting these results since CFR-based estimates are more uncertain than multi-cause mortality data approaches. However, these are consistent with estimates of neonatal deaths due to direct complications of preterm birth in 2010 (1.1 million (2) or 0.84 million (36)) when combined with previous global estimates of the indirect effect of preterm birth (4,51). Deaths among neonates born at <32 wk are most likely to be coded (correctly) as direct preterm deaths, and the CFR approach suggest ~1.2 million which is within the uncertainty range of the current estimates. Currently, even in high-income countries with good vital registration systems, live-births at <28 wk are often classified as nonviable miscarriages (52). Neonatal deaths in those born at 32–36 wk are more likely to be coded (appropriately) to other causes, such as infection, with prematurity as a risk factor. Our finding suggests that two-third of all neonatal deaths may be in those born preterm, in line with previous global estimates and with the United States, where preterm birth is a direct cause of 36% of all infant deaths, but two-thirds of all infant deaths were among babies who were born preterm (53). A formal
comparative risk factor analysis would be of value and should be linked with assessment of Small for Gestational Age (54). The majority of preterm babies survive without impairment, but at <28 wk gestation, over half (52%) are estimated to have some long-term impairment if they survive the neonatal period (Figure 7). Worldwide in 2010, 5% of those born at 32–36 wk who survive the neonatal period are estimated to have some degree of long-term impairment, but this includes 85% of all 15 million preterm births, and hence, their contribution to the overall burden is substantial (45,46). However, global averages mask considerable regional differences: 52% of all live births, 60% of preterm births, and 75% of neonatal deaths in those preterm born are estimated to occur in sub-Saharan Africa and South Asia but only 46% of impaired postneonatal survivors (Figure 8). A baby born alive before 32 wk of gestation has a 53% chance of surviving the neonatal period without later neurodevelopmental impairment in high-income regions, as compared with just 27% if born in South Asia or sub-Saharan Africa. These differences are mainly due to a marked survival gap and access to neonatal care between low- and high-income regions. The burden of impairment is disproportionately heavier in middle-income regions, which account for 33% of preterm births, 23% of the deaths, but 43% of the impairment. In countries scaling up NICU, urgent attention to quality of care is required to minimize impairment.

These estimates considered a defined group of neurodevelopmental disorders only, long-term sequelae of preterm birth are much wider than these. Many studies have reported an association of preterm birth with specific learning and executive function impairments and adverse mental health outcomes, including attention-deficit hyperactivity disorders, autistic spectrum disorders, anxiety/emotional disorders, and probably schizophrenia, particularly in those born very preterm (55–68). These deficits are also increasingly being recognized in late preterm infants (27,37,69–73).

A large population-based cohort study in the United Kingdom reported that as well as neurodevelopmental impairment other health outcomes were worse in those born preterm at any gestation than their term-born peers (38). Preterm birth at all gestations is linked to adverse long-term respiratory and cardiovascular outcomes (74,75). Babies who develop chronic lung disease after bronchopulmonary dysplasia have reduced lung function and lower exercise tolerance, placing them at higher risk of symptomatic chronic obstructive disease in middle adulthood than a term-born child (76–78). Even in the absence of chronic lung disease, preterm-born children were also more likely to have asthma and reduced lung function at school age as compared with their term-born peers (38,79).

A recent meta-analysis shows that preterm birth is associated with substantially higher blood pressure in adult life and with early onset of other features of the metabolic syndrome (80,81). Given the burgeoning prevalence of noncommunicable diseases worldwide, this additional contribution of preterm birth to the major noncommunicable diseases of adult life, and global clinical and economic burden, is worthy of strong emphasis.

Time Trends
In most countries with reliable data, preterm birth rates remain constant or are increasing; this coupled with population growth will mean increasing numbers of preterm births each year (1,82). Changes in perinatal care over the past 50 y have been substantial, and few countries have data on rates of impairment in preterm birth survivors across all gestational
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Data Limitations
Data availability varied with the least data from the highest burden settings. This is common to all the conditions considered in this supplement. Data on postneonatal child mortality (1–59 mo) after preterm birth were very sparse, especially from low-income settings, and it was not possible to estimate the number of survivors till the age of 5 years. We therefore applied the risk of impairment in those followed up at 2–5 y of age to all postneonatal survivors. Data were especially limited regarding the neurodevelopmental impairment. Published data on neurodevelopmental outcomes 2–5 y after preterm birth are not yet available for those born in 2010. We therefore have relied on outcome data for those born earlier in the decade. For neonates receiving NICU care in high- and intermediate-mortality settings, few data were available. We explored the use of historical data from the 1980s in high-income countries before the widespread use of antenatal corticosteroids and surfactant; however, we elected to use the limited recent data from these high burden populations (Supplementary Information online). No data are available for those preterm postneonatal survivors who did not have access to NICU care who are likely to be at higher risk than the general term-born population. We conservatively applied the population risk of impairment for late preterm as a minimum biological risk (30). Historical data of the impairment risk in countries before modern NICU care suggest that the risk may be substantially higher than this (Supplementary Information online) (85).

Despite recent interest in moderate and late preterm births (32–33 and 34–36 wk, respectively), descriptive studies are heterogeneous in design, mainly from high-income countries and focused on more common, milder behavioral and school impairment outcomes (70,71). Limited recent population-based data were available on absolute risk of impairment, and our estimates for late and moderate preterm outcomes are based on only two population-based cohorts (30,31). Although isolated mild motor impairment and mild motor impairment with cognitive impairment were taken into account, isolated cognitive impairment was not considered in estimating YLDs in GBD2010 for neonatal conditions. This is the most common outcome after extremely preterm birth and will be included in the future continuous GBD updates (86).

We included the sex of the baby in our assessment of prevalence of preterm birth, as this may influence survival and impairment outcomes: preterm-born males are more likely to die or survive impaired at any given gestational age (19,25,83,87). However, insufficient data were available to be able to quantify the sex differences at each subsequent step of the model.

One notable challenge is the assessment of gestational age. The use of birth weight proxies may misclassify half of appropriately grown 27 wk babies who weigh >1,000 g, while misclassifying in the opposite direction more mature babies who are small for gestational age. In high-mortality settings, there may be a high proportion of babies who were over 28 wk and small for gestational age among survivors (88,89). An important priority is the development of accurate, practical tools to assess gestational age in low- and middle-income settings to increase the availability of data on outcome after preterm birth in these settings.

Data Improvement
The introduction and scale-up of neonatal intensive care in the United Kingdom in the 1970s prompted investment in follow-up studies of NICU graduates (90). The need for information on long-term outcome remains critical not only for health-care planning but also for parents, particularly with ever advancing technologies in high-resource settings, and the scale-up of neonatal intensive care across middle income countries, with adoption in some low-income countries, especially in the private sector.

Preterm birth is a syndrome (91), and we expect outcomes to vary by underlying cause, with different outcomes from preterm labor/ruptured membranes (associated with infection), fetal growth restriction, preeclampsia, and provider-initiated preterm births as compared with those with rapid delivery following abrupton or cervical incompetence. The proportion impaired at any given gestational age may therefore vary between populations with different risk factors and cause profiles and recording a minimum level of granularity as to the preterm birth phenotype may improve data comparability (91).

The same factors leading to preterm birth can also affect the baby’s long-term outcome. Long-term outcomes are influenced by complex interactions between biological, medical, social, familial, and environmental factors, and their influence on the dynamic and adaptive maturational process of brain development (28,92–94). Well-designed studies, capturing biological and social covariates, are required. The cohorts we identified showed substantial heterogeneity in context, care practices, and outcome reporting, for example, by birth weight or gestational age, at different ages of follow-up, using different assessment techniques and with variable rates of loss to follow-up (95). Some studies have reported higher rates of severe disability in those lost to follow-up, resulting in ascertainment bias (96–99). More consistent and comprehensive tools and methods for describing outcomes, including milder behavioral and specific learning impairments are needed so that interventions can be targeted appropriately and findings across studies can be directly compared.

Programmatic Implications
This analysis has highlighted major geographical inequalities for babies’ outcomes and in the data to track these outcomes. There are three very different worlds that preterm babies are born into (5), reflecting a transition from high neonatal...
Prevention of preterm birth is a knowledge gap given few evidence-based, high-impact options. Even in high-income settings, the available approaches are challenging to implement and lead only to modest reductions in preterm birth (82). Early intervention with more focus on the social determinants of health—e.g., improving the nutritional status of female children, retaining adolescent girls in school, family planning, gender empowerment, smoking cessation, and in reduction in infections e.g., HIV and malaria on a population level—may have some benefit (101). However, strategic research is required to better understand and address the complex interplay between genetic and environmental factors leading to preterm birth (44).

Reducing deaths and long-term impairment among preterm babies will require improved coverage of quality maternity and overall neonatal care in all settings. This is challenging but is likely to be more cost effective than focusing on highly specialized neonatal intensive care in isolation (5). This will need changes in societal norms and culture—for example, improved maternal health; regular-quality antenatal care commencing early in pregnancy; high-quality facility birth with antenatal steroids to assist lung maturation if required (102); and essential newborn care, Kangaroo care, and postnatal visits.

Systems to improve follow-up of preterm babies will be important to track the global burden and to allow appropriate prioritization of resources for health, education, and social care of those preterm born with disability. Priority has been placed in tracking outcomes of extreme preterm birth with the highest individual risk and more recently the relatively larger numbers of those born late preterm (34–36 wk). However, those born between 27 and 33 wk are a considerable public health burden—we estimate nearly three times as many impaired postneonatal survivors after preterm birth at 28–31 wk as compared with those <28 wk.

Investment in early years of research is likely to reap lifelong personal and economic benefits yet newborns and children remain underrepresented in research priorities (103).

Table 4. Research in context regarding the burden of preterm birth

| Data findings | Preterm birth, before 37 completed weeks, presents a large burden worldwide with 15 million babies affecting in 2010 accounting directly and indirectly for an estimated 2.0 million (uncertainty range 1.9–2.2 million) neonatal deaths and for 0.9 million (uncertainty range 0.8–1.1 million) impaired survivors, 3.2% of the entire GBD. |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Data for action | Key programs priorities include:                                                                                                                                                                   |
|               | Prevention of preterm birth must be strategically addressed; current solutions offer limited proof of impact. Urgent investments are required: in basic science regarding the causes of spontaneous preterm birth, in developing innovative solutions, and in better understanding of the patterns in low-income countries where infections and other risks are more prevalent. |
|               | Prevention of deaths and disability: Immediate burden reduction is possible through increasing coverage and the quality of care around the time of birth and in the postnatal period for women in preterm labor and their preterm babies. |
|               | Identification and care of survivors with disability.                                                                                                                                              |
| Data gaps and improvements | Major gaps were found in the quantity and the quality of data to inform these estimates including:                                                                                               |
|               | Geographic gaps especially for high burden settings and population-based data.                                                                                                                                 |
|               | Limitations in accuracy of assessment and reporting of gestational age, especially in settings without routine early ultrasound scanning in pregnancy.                                                                 |
|               | Challenging data on impairment outcomes with variable metrics and tools across studies administered at different ages, further affected by high loss to follow-up in many cohort studies.                                |
|               | Actions/possible solutions: Increased awareness of the importance of gestational age assessments, and availability of simplified, low-cost gestational age assessment tools. Standardized reporting of impairment outcomes using, validated across settings. |
Conclusions
Preterm birth presents a large burden worldwide in terms of mortality and long-term physical and mental health and neurodevelopmental impairment throughout later life. The data are least available where the burden is heaviest. Improved data collection, particularly from low- and middle-income countries, with standardization of assessment tools is needed to track this burden and evaluate the effectiveness of interventions targeting preterm births (Table 4).

Improved care for preterm babies would reduce mortality especially in low-income countries, and this is still the largest part of the burden worldwide. Most babies who survive (>90%) are not impaired, and the current burden of disability could be reduced especially in middle-income settings improving the quality of neonatal care. Prevention of preterm birth should be a longer term priority, but major reduction in the global burden of mortality and morbidity following preterm birth could be made immediately with improved coverage and quality of care.

SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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APPENDIX. TRENDS IN SURVIVAL AND MORBIDITY OF THE MOST PRETERM BABIES (<26 WEEKS) IN HIGH-INCOME COUNTRIES
Survival for babies with very low gestational ages (24–26 weeks) has increased with 80% survival at 25 weeks, although mortality and morbidity remains very high at the lower gestations (a). However, wide variation in survival rates exist, with the highest survival in very centralized services and where appropriate interventions to improve fetal and neonatal condition are used – such as antenatal corticosteroids, occlusive wrapping to prevent heat loss after birth and surfactant replacement therapy. Below 25 weeks outcome data are confounded by public policy and actual practice in the provision of care.

Disability free survival is around 60% at 26 weeks, 10% have severe disability at 3 years, and the proportion with disability rises at 25 weeks and below, as shown in national data in England for 2006 (b) (84). As these children survive for longer increasing proportions are found to have special educational needs and psychiatric problems (42,63).

The incremental costs attributable to preterm birth rise steeply at very low gestations (c). The costs are primarily attributable to neonatal intensive care due to prolonged hospital stay in survivors, discharge being at around 40 weeks postmenstrual age, giving an average of 4 months care for the most immature. Later special educational special needs add lower costs but over a long time period.
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