Linking Birth Outcomes to Diabetes Mellitus
An Exploratory Review

September 2014

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ABOUT SPRING

The Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) project is a five-year USAID-funded Cooperative Agreement to strengthen global and country efforts to scale up high-impact nutrition practices and policies and improve maternal and child nutrition outcomes. The project is managed by JSI Research & Training Institute, Inc., with partners Helen Keller International, The Manoff Group, Save the Children, and the International Food Policy Research Institute. SPRING provides state-of-the-art technical support and focuses on the prevention of stunting and maternal and child anemia in the first 1,000 days.

RECOMMENDED CITATION


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SPRING

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<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BW</td>
<td>birthweight</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>ELN-NCD</td>
<td>Early-Life Nutrition Linkages to Noncommunicable Disease</td>
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<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
</tr>
<tr>
<td>IR</td>
<td>insulin resistance</td>
</tr>
<tr>
<td>LBW</td>
<td>low birthweight</td>
</tr>
<tr>
<td>LMICs</td>
<td>low- and middle-income countries</td>
</tr>
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<td>MMS</td>
<td>multiple micronutrient supplementation</td>
</tr>
<tr>
<td>SPRING</td>
<td>Strengthening Partnerships, Results, and Innovations in Nutrition Globally</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

This review describes the evidence linking birth outcomes to risk of developing diabetes mellitus (DM). DM prevalence is increasing unacceptably, especially in low- and middle-income countries (LMICs), placing a heavy burden of morbidity on individuals and driving higher health care costs and lower productivity.

This review was conducted as part of the Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) project’s work on the “Early-Life Nutrition Linkages to Noncommunicable Disease” (ELN-NCD) simulation model. The ELN-NCD simulation model examines how birth outcomes relate to later life risk of nutrition-related NCDs. The final model focuses only on cardiovascular disease, but during the systematic evidence review, a substantial body of literature was found on linkages between birth outcomes and DM.

Twenty-three articles were reviewed and are analyzed here. A majority of studies found increased risk of DM and/or pre-DM conditions (fasting glucose, fasting insulin) with lower birthweight (BW), and some studies found a U-shaped relationship, meaning that at a certain BW, the risk of DM begins to increase again. SPRING’s earlier ELN-NCD work models mortality and morbidity from later life cardiovascular disease associated with early-life undernutrition. In the case of DM, it is more difficult to make such estimations of reductions in mortality and morbidity. While it appears that the majority of the studies found a significant inverse relationship between BW (below a certain threshold) and DM risk, there is variance in the nature of the relationship, how persistent it is throughout the life cycle, and what modifies the risk. Also, the relationship is difficult relationship to understand because DM has a multifactorial and dynamic etiology, including strong contributions from childhood and adult body weight trajectory, lifestyle, and genetic factors.

Consensus is growing that BW does have significant effect on DM risk, but more work is needed to conclusively define that association in LMICs, in different ethnic groups, and across the spectrum of BW. Efforts to reduce low birthweight (LBW) should continue, given its proven relationship with neonatal mortality; this review’s attempt to improve estimates of the relationship between LBW and later life NCD risk should be considered further support to bolster the case for efforts to reduce LBW.

INTRODUCTION

This review describes the evidence linking birth outcomes to risk of developing diabetes mellitus (DM, or Type 2 diabetes). Globally, prevalence of DM among adults (aged 20–79 years) was estimated to be about six percent in 2010, affecting 285 million adults (Shaw, Sicree, and Zimmet 2010). This is expected to increase to just under eight percent (439 million adults) by 2030, with the majority of the growth in low- and middle-income countries (LMICs). There is
general consensus that the rising tide of DM is unacceptable: the disease places a heavy burden of morbidity on individuals and is one of the major drivers of health care costs and lost productivity (The Lancet 2014).

While relatively few individuals with DM will die directly from an imbalance in glucose or other metabolic imbalances (Zargar et al. 1999), the disease is a risk factor for more terminal conditions, such as stroke, heart failure, and renal failure (Peters, Huxley, and Woodward 2014; Holman, Sourij, and Califf 2014; Perneger et al. 1994; Yoon et al. 2006). DM is also an identified risk factor for several types of cancer, though the mechanism by which it increases risk is not entirely understood (Shi and Hu 2014). This is further complicated by the differentials in risk for early- and late-onset DM (S.H. Song and Hardisty 2008).

There is a progression of conditions that can lead to onset of DM, including obesity, insulin resistance, and impaired glucose tolerance. The general constellation of pre-DM conditions can be roughly mapped (Figure 1); however, this process is not linear, and an individual can manifest any of these conditions out of this sequence, or stop progression prior to onset of DM.

One can develop DM from any stage in Figure 1, though the risk appears to be higher as these symptoms progress (Sung et al. 2012). The focus of efforts to prevent DM and pre-DM conditions has been on adolescent or adult interventions to improve diet and increase exercise (Ley et al. 2014); however, in other areas of research, notably obesity reduction, few studies have been able to show sustained, long-term improvements due to improved diet and exercise regimes (Monasta et al. 2011; Ho et al. 2013; Curioni and Lourenço 2005). Many more studies have devoted time to treatment options for DM via pharmacology (e.g., Li et al. 2010).
More recently, a small body of evidence has emerged around reduction of DM risk via improving birth outcomes, as part of the life course hypothesis that an individual’s metabolism is affected by conditions in utero (Godfrey, Gluckman, and Hanson 2010). Hattersley and Tooke (1999) coined the term “fetal insulin hypothesis.” Birth outcomes such as LBW, preterm birth, or small for gestational age have been linked to adult DM, either directly or through prediabetic conditions at various stages of infancy, adolescence, and adulthood (e.g. Kaijser et al. 2009; Whincup et al. 2008; Tinnion et al. 2013).

This review will summarize the current state of evidence on the associations between birth outcomes and DM or pre-DM conditions (such as insulin resistance or impaired glucose tolerance). It will also provide information on some of the primary post-birth modifiers of DM risk.

**METHODS**

This review was conducted as part of the Strengthening Partnerships, Results, and Innovations in Nutrition Globally (SPRING) project’s work on the “Early-Life Nutrition Linkages to Noncommunicable Disease” (ELN-NCD) simulation model. The ELN-NCD simulation model examines how birth outcomes relate to later life risk of nutrition-related NCDs. The final model focuses only on cardiovascular disease, but during the systematic evidence review, a substantial body of literature was found on linkages between birth outcomes to DM.

Evidence was collected via a systematic stand-alone review of all evidence related to the “hub” of birth outcomes and impact on risk of DM or pre-DM conditions. The focus was specifically on BW, not small for gestational age or preterm birth; however, if an article examined one of these conditions in addition to LBW, it was included.

The primary pre-DM conditions used in the literature were:

- insulin resistance (IR)
- impaired glucose tolerance (IGT)
- elevated fasting glucose
- elevated fasting insulin
- metabolic syndrome\(^1\)

The search was conducted via Google Scholar for English-language articles from the past 20 years that included the search terms listed in the Annex. Articles from LMIC countries were preferred, but no study was excluded if it was from a high-income country. After all terms were

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\(^1\) This measure is a combined indicator of high glucose plus cholesterol, blood pressure, and waist circumference. It is used primarily to predict increased risk for heart disease and other health problems, such as diabetes and stroke.
exhausted, articles were ranked based on quality and location. If a study had a particularly small sample size (<100); a lack of statistical rigor (no control group or lacked tests of significant difference); or shortcomings in reporting of results (did not report sufficient information to glean risk ratios, or raised concern on the design of the study), it was excluded from the final review tables.

Extraction of information was done for all eligible studies and formed the basis for the tables in this review.

**RESULTS OF REVIEW**

Twenty-five articles were found that met the search criteria. Four of the 27 articles found were excluded due to sample size or reporting issues (Sugihara et al. 2008; Choi et al. 2000; Anazawa, Atsumi, and Matsuoka 2003; Yajnik 2002). Other relevant reviews using gestational age as an outcome were found, but they were excluded from this review as they did not fit the search criteria of using BW as the hub for the risk estimation. (See Parkinson et al. 2013; Tinnion et al. 2013; Darendeliler et al. 2008 for more information on these alternative measures of birth outcomes).

Another set of literature focused on large for gestational age or high BW, a condition often caused by gestational diabetes (Boney et al. 2005; Carpenter 2007). Due to the frequent complication of gestational diabetes, these studies were not summarized here for equal comparison against the evidence for LBW; however, they were included if the primary purpose of that study was to review BW or LBW.

In the remaining 23 studies found in the review, the following measures of BW outcomes were used:

- Continuous measure of BW
- Categorical measure of BW (groupings of kg or g measures)
- A binary measure of BW (LBW, <2,500g)/normal BW)

Four of the included studies were systematic reviews of the topic and pull from a larger population for their risk estimates (three of the four included some form of meta-analysis). The rest of the studies employed a wide range of methods to develop their estimates, including retrospective chart review, longitudinal pre- and post- designs, as well as prospective birth cohort studies.

**Relationship with Risk**

A majority of studies found increased risk of DM and/or pre-DM conditions (fasting glucose, fasting insulin) with lower BW (see Table 1). Of the 23 studies, 11 found unambiguous inverse
associations with BW; that is, as BW increased, risk of developing a DM or a pre-DM condition appeared to go down. An additional four studies found an inverse relationship when adult weight, waist circumference, or BMI were controlled for. Four more studies saw an inverse association with insulin resistance, but they documented non-significant associations with other pre-DM conditions (Fall et al. [1998] only saw this association in men). This association appeared more often when the studies’ focus was on DM outcomes (top of Table 1), less so with pre-DM conditions (bottom of Table 1). However, few studies reported whether they tested for anything other than a linear trend, which imposes a heavy assumption on the shape of the trend over the full range of BW.
Table 1. Relationship between BW and DM or Pre-DM Condition

<table>
<thead>
<tr>
<th>#</th>
<th>Author-Date</th>
<th>Birth Outcome</th>
<th>Outcome Type</th>
<th>Location</th>
<th>Diabetes Outcome</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bonsdorff et al. 2013</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Iceland</td>
<td>DM</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Curhan et al. 1996</td>
<td>BW (lbs)</td>
<td>(categorical)</td>
<td>USA</td>
<td>DM</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Fall et al. 1998</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>India</td>
<td>DM</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Harder et al. 2007</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Review; Various</td>
<td>DM</td>
<td>U-shaped</td>
</tr>
<tr>
<td>5</td>
<td>Kaijser et al. 2009</td>
<td>BW (g)</td>
<td>(continuous)</td>
<td>Sweden</td>
<td>DM</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>Newsome et al. 2003</td>
<td>BW (multi)</td>
<td>multi</td>
<td>Review; Various</td>
<td>DM</td>
<td>- (after adjusting for current weight)</td>
</tr>
<tr>
<td>7</td>
<td>Norris et al. 2012</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>Brazil, Guatemala, India, the Philippines, and South Africa</td>
<td>DM/fasting glucose</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>Phipps et al. 1993</td>
<td>BW (kg)</td>
<td>(categorical)</td>
<td>UK</td>
<td>DM</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>Raghupathy et al. 2010</td>
<td>BW (z-score)</td>
<td>(continuous)</td>
<td>India</td>
<td>DM/ IGT</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Song et al. 2012</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Review; Various</td>
<td>DM</td>
<td>U-shaped</td>
</tr>
<tr>
<td>11</td>
<td>Tian et al. 2006</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>China</td>
<td>DM</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Wei et al. 2003</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Taiwan</td>
<td>DM</td>
<td>U-shaped</td>
</tr>
<tr>
<td>13</td>
<td>Whincup et al. 2008</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>Review; Various</td>
<td>DM</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Bavdekar et al. 1999</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>India</td>
<td>fasting insulin/ IR, fasting glucose</td>
<td>- , 0</td>
</tr>
<tr>
<td>15</td>
<td>Bhargava et al. 2004</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>India</td>
<td>IGT, fasting insulin, IR</td>
<td>0, -,-</td>
</tr>
<tr>
<td>#</td>
<td>Author-Date</td>
<td>Birth Outcome</td>
<td>Outcome Type</td>
<td>Location</td>
<td>Diabetes Outcome</td>
<td>Relationship</td>
</tr>
<tr>
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<td>---------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>16</td>
<td>Bonsdorff et al. 2013</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Iceland</td>
<td>IR, fasting glucose, DM</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>Fall et al. 1995</td>
<td>BW (lbs)</td>
<td>(continuous)</td>
<td>UK</td>
<td>fasting glucose</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>Fall et al. 1998</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>India</td>
<td>IR</td>
<td>- (men), 0 (women)</td>
</tr>
<tr>
<td>19</td>
<td>Frontini et al. 2004</td>
<td>LBW/NBW (g)</td>
<td>(binary)</td>
<td>USA</td>
<td>fasting glucose, IR</td>
<td>0, -</td>
</tr>
<tr>
<td>20</td>
<td>Hovi et al. 2007</td>
<td>VLBW (g)</td>
<td>(binary)</td>
<td>USA</td>
<td>IR, IGT</td>
<td>- , -</td>
</tr>
<tr>
<td>21</td>
<td>Mi et al. 2000</td>
<td>BW (g)</td>
<td>(continuous)</td>
<td>China</td>
<td>fasting glucose</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Newcombe et al. 2003</td>
<td>BW (multi)</td>
<td>multi</td>
<td>Review; Various</td>
<td>IR</td>
<td>- (after adjusting for current weight)</td>
</tr>
<tr>
<td>7</td>
<td>Norris et al. 2012</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>Brazil, Guatemala, India, the Philippines, and South Africa</td>
<td>IR</td>
<td>- (after controlling for Adult waist circumference)</td>
</tr>
<tr>
<td>9</td>
<td>Raghupathy et al. 2010</td>
<td>BW (z-score)</td>
<td>(continuous)</td>
<td>India</td>
<td>IR</td>
<td>- (after controlling for Adult BMI)</td>
</tr>
<tr>
<td>22</td>
<td>Stein et al. 2002</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>Guatemala</td>
<td>fasting glucose</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>Stewart et al. 2010</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>Nepal</td>
<td>IR &amp; fasting glucose</td>
<td>0, 0</td>
</tr>
<tr>
<td>15</td>
<td>Curhan et al. 1996</td>
<td>BW (lbs)</td>
<td>(categorical)</td>
<td>USA</td>
<td>diabetes mellitus</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>Fall et al. 1998</td>
<td>BW (kg)</td>
<td>(continuous)</td>
<td>India</td>
<td>diabetes mellitus</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Harder et al. 2007</td>
<td>BW (g)</td>
<td>(categorical)</td>
<td>Review; Various</td>
<td>diabetes mellitus</td>
<td>U-shaped</td>
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<tr>
<td>7</td>
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</tr>
<tr>
<td>17</td>
<td>Newcombe et al. 2003</td>
<td>BW (multi)</td>
<td>multi</td>
<td>Review; Various</td>
<td>diabetes mellitus</td>
<td>- (after adjusting for current weight)</td>
</tr>
</tbody>
</table>

Insulin resistance is primarily measured by doing a HOMA-IR or RIR-HOMA test.

* According to this study, “There were no direct associations between adult glucose intolerance and newborn size, or size in infancy, but after adjusting for adult BMI and lifestyle factors, smaller size at birth was associated with a higher risk of adult IGT/DM.”

**This measure is a combined indicator of high glucose plus cholesterol, blood pressure, and waist circumference. It is used primarily to predict increased risk for heart disease and other health problems, such as diabetes and stroke.

11 | Linking Birth Outcomes to Diabetes Mellitus: An Exploratory Review
In fact, when looking at the four literature reviews included in this review, two of the studies found evidence of a nonlinear, U-shaped relationship. This means that at a certain BW, the risk of DM plateaus and begins to increase again (Harder et al. 2007; Y. Song et al. 2012). The remaining two, both meta-analyses, found an inverse relationship overall but mentioned a subsection of studies that had U-shaped relationships (Newsome et al. 2003; Whincup et al. 2008). Whincup et al. (2008) in particular noted that U-shaped results occurred in the three Native American population studies included in the review; they were excluded in the final meta-analysis to reduce heterogeneity.

There are two primary explanations posited for this mix of findings.

1. **Differences in starting BW in different levels of economic prosperity, shifting the distribution of children falling into the low, normal, and high BW categories.** In LMICs, a greater proportion of babies will fall in the LBW category, while in high-income or food-secure countries, the distribution will include more high BW babies. Indeed, two of the studies supporting a U-shaped relationship (Harder et al. 2007; Y. Song et al. 2012) were reviews that included several high-income country studies; a third single study (Wei et al. 2003) also found a U-shaped association in a Taiwanese population.

2. **Differences in risk for different ethnicities.** Some evidence showed that certain ethnicities are at greater risk of gestational diabetes and other maternal metabolic imbalances that could lead to macrosomia (babies born at or above 4,000g). These imbalances also carry an independent risk for metabolic disorder, which could confound the results for high BW (Dornhorst et al. 1992).

Table 2 gives approximate odds ratios and turning points for this association found in the four systematic reviews.
### Table 2. Odds Ratios and Turning Points from Four Systematic Reviews

<table>
<thead>
<tr>
<th>Author of Review (in order of recency)</th>
<th>DM-Specific Outcomes?</th>
<th>Type of Association</th>
<th>Number of Studies Included</th>
<th>OR (BW&lt;2,500g)</th>
<th>OR (BW&gt;4,000g)</th>
<th>Turning Point (if continuous relationship)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newsome et al. 2003</td>
<td>Yes</td>
<td>Inverse</td>
<td>48</td>
<td>not calculated</td>
<td>not calculated</td>
<td>not calculated</td>
</tr>
<tr>
<td>Harder et al. 2007</td>
<td>Yes</td>
<td>U-Shaped</td>
<td>14</td>
<td>1.47</td>
<td>1.36</td>
<td>Using smaller weight breakdowns, lowest risk was found for BW of between 3,500 and 4,000g.</td>
</tr>
<tr>
<td>Whincup et al. 2008</td>
<td>Yes</td>
<td>Inverse</td>
<td>30 (14 for meta-analysis)</td>
<td>0.80 for every 1 kg increase</td>
<td>Of six subsets explored, 4 North American subpopulations showed a u-shaped relationship, with turning points between ~2,750 and 3,500g.</td>
<td></td>
</tr>
<tr>
<td>Y. Song et al. 2012</td>
<td>yes</td>
<td>U-Shaped</td>
<td>23 for meta-analysis</td>
<td>0.78 for every 1 kg increase</td>
<td>Study did not conduct analysis to test for nonlinear relationship; rather it concluded from the evidence in other studies that the relationship between BW and DM risk is inverse and linear until 4,000g, at which point risk flattens and begins to increase again.</td>
<td></td>
</tr>
</tbody>
</table>

Except for in the studies on Native American populations, it appears the turning point for the relationship occurs at a relatively high BW. For example, looking at the latest available national BW surveys for two Southeast Asian countries, BW above 3,000g occurs rarely (Subramanyam, Ackerson, and Subramanian 2010; Bangladesh Bureau of Statistics and UNICEF 2005). This suggests that for LMICs, particularly those in Southeast Asia, there are too few babies being born at higher BW for the U-shaped relationship to be observed. Given the results, it is important to keep in mind the context of the population before assuming a relationship between BW and DM risk.

### Potential Mediating Factors

**Sex**

When studies disaggregated analysis for child’s sex, the majority found no significant differences. A 2003 review of 48 studies that included risk disaggregated by sex found similar rates regardless of gender (Newsome et al. 2003). However, some evidence from other single studies showed that for certain populations, there may be greater variation. (Fall et al. 1995) found the relationship between BW and fasting glucose and insulin to be much stronger in
women than men in England, while (Fall et al. 1998) found the opposite to be true in Mysore, India.

**Gestational Age**

Reflecting the current debate on what aspect of gestation drives the association with DM risk, several of the studies included controls for gestational age, fetal growth restriction, and birth length. For instance, (Phipps et al. 1993) found that the trends with BW were independent of gestational age, which was not found to be a significant predictor of risk. (Kaijser et al. 2009) confirmed an inverse association between BW and DM. The study also found an independent association between increased DM risk and preterm birth and fetal growth restriction. This suggests that if an infant is affected by both conditions, his or her risk would be multiplicative for DM.

**Type, Rate, and Timing of Weight Gain**

There also appears to be a significant effect on the relationship between LBW and DM risk in the presence of higher relative weight in later childhood, adolescence, or adulthood (Bavdekar et al. 1999; Raghupathy et al. 2010). Those born with LBW could potentially have a higher propensity of becoming overweight later in life; however, current evidence suggests that those born with high BW are at risk of becoming overweight, not those born with LBW (Baird et al. 2005). Studies in this area overwhelmingly come from developed countries, thus they cannot reflect the dynamics in the context of nutrition transition. Some evidence showed that regardless of total weight, when those born with LBW gain weight, it is more likely to be abdominal weight gain, a risk factor for metabolic imbalance (Schroeder, Martorell, and Flores 1999). Independence of effect was tested in several studies by adjusting for later-life BMI, which strengthened the association between LBW and DM (Newsome et al. 2003; Whincup et al. 2008).

In addition, analysis in a separate set of studies was extended to consider later-life weight gain on the association between BW and DM risk. These selected studies are described in Table 3. While not unanimous, the majority of these studies found an independent increased risk for developing DM among: a) those who had higher weight in later life (Adair et al. 2013; Crowther et al. 1998; Bonsdorff et al. 2013), and b) those who had more rapid weight gain in later life (Norris et al. 2012; Bhargava et al. 2004; Crowther et al. 1998). When combined, these results suggest that those most at risk of DM or pre-DM conditions are those born with LBW, who then gain weight at a rapid pace and attain a higher weight later in life relative to their peers.
<table>
<thead>
<tr>
<th>Author – Date</th>
<th>Location</th>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>Adair et al. 2013</td>
<td>Brazil, Guatemala, India, the Philippines, and South Africa</td>
<td>Fasting glucose, dysglycemia (IGT or DM)</td>
<td>Conditional weight &amp; height (deviation from expected size based on own previous measures/child cohort - represents faster or slower relative weight gain)</td>
<td>Lower birthweight increased risk of dysglycemia (0.89 [0.81—0.98]), but linear growth and relative weight gain in childhood were not associated with dysglycemia. Adult conditional relative weight was also associated with dysglycemia (1.32 [1.20–1.45]). (ADD HEIGHT)</td>
</tr>
<tr>
<td>Sun et al. 2008</td>
<td>USA</td>
<td>Metabolic syndrome</td>
<td>BMI</td>
<td>They found birthweight significantly and positively affects child BMI, which in turn positively affects adult obesity and risk of metabolic syndrome. The earliest age at which child weight diverged between the MS and non-MS group, independent of birthweight, was 8 years old for boys and 13 years old for girls.</td>
</tr>
<tr>
<td>Crowther et al. 1998</td>
<td>South Africa</td>
<td>Fasting insulin, IR</td>
<td>BMI</td>
<td>Children born with LBW but who had high BMI at 7 years had higher insulin concentrations compared with those with LBW and low BMI at 7 years. There were also positive correlations between weight velocity and insulin resistance.</td>
</tr>
<tr>
<td>Bavdekar et al. 1999</td>
<td>India</td>
<td>IR</td>
<td>Height/BMI</td>
<td>Taller height at 8 years predicted insulin resistance; the most insulin-resistant children were those who had short parents but had grown tall. The interaction of weight at eight years and birthweight was significant, with the LBW children who were now heaviest at higher risk for insulin resistance.</td>
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<tr>
<td>Author – Date</td>
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<tr>
<td>Bhargava et al. 2004</td>
<td>India</td>
<td>IGT, DM</td>
<td>BMI &amp; age at adiposity rebound</td>
<td>Those with IGT/DM typically had a low BMI up to two years of age, followed by an early adiposity rebound (the age after infancy when body mass starts to rise) and an accelerated increase in body-mass index until adulthood.</td>
</tr>
<tr>
<td>Fall et al. 2008</td>
<td>India</td>
<td>IGT, DM, IR, Metabolic syndrome</td>
<td>BMI &amp; age at adiposity rebound</td>
<td>Greater infant BMI/weight gain was associated with a lower risk of DM, especially in LBW infants, but it was also associated with an increased risk of metabolic syndrome and its components, a paradoxical finding that may be explained by the cohort’s body composition during different age periods. Rapid BMI gain during childhood and adolescence was a risk factor for both disorders.</td>
</tr>
<tr>
<td>Norris et al. 2012</td>
<td>Brazil, Guatemala, India, the Philippines, and South Africa</td>
<td>Fasting glucose/DM, IR</td>
<td>Conditional weight gain (deviation from expected size based on own previous measures/child cohort – represents faster or slower relative weight gain)</td>
<td>LBW and accelerated weight gain after 48 months are risk factors for adult glucose intolerance; greater CWG at 0–24 and 24–48 months and 48 months–adulthood predicted higher IR (all P &lt; 0.001). Accelerated weight gain between 0 and 24 months did not predict glucose intolerance until adult waist circumference was controlled for, then it had an inverse association with fasting glucose/DM.</td>
</tr>
<tr>
<td>Bonsdorff et al. 2013</td>
<td>Iceland</td>
<td>IR, DM</td>
<td>BMI</td>
<td>Compared with those with high birth weight and low BMI in midlife, the odds of diabetes was almost fivefold for individuals with low birth weight and high BMI (OR, 4.93; 95% CI, 2.14–11.37). Excessive weight gain in adulthood might be particularly detrimental to the health of old individuals with low birth weight.</td>
</tr>
</tbody>
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16 | Linking Birth Outcomes to Diabetes Mellitus: An Exploratory Review
Although there is sufficient evidence to state that there is likely a compound risk of LBW, rapid weight gain, and high BMI in later life, it is unclear exactly when it is most risky for weight gain to occur during a person’s life. In the studies selected for this review, the age range for weight gain spans from one month to greater than 70 years. Findings were inconsistent for the risk in the late childhood–later adolescence period.

Some recent studies found no additional risk when weight gain occurred in the first two to four years of life (and in some cases, a very small protective effect for those born with LBW) but increased risk when additional weight gain occurred after that period (Norris et al. 2012; Bhargava et al. 2004; Fall et al. 2008). However, a separate literature review summarizing another set of evidence found DM risk beginning within the first two years of life, in some cases as early as the first six months (Y. Song et al. 2012).

Risk of DM and pre-DM conditions may also increase in the adolescent period (Bavdekar et al. 1999; Sun et al. 2008; Crowther et al. 1998). In a large study from Finland, the association with weight gain became significant in the seven- to 15-year-old period; the relationship to development of DM was strongest among those children born below 3,000g (Forsén et al. 2000). In yet another set of literature, the strongest, most significant effects occurred when weight gain or high BMI occurred in adulthood; however, one study found no effects prior to adulthood, while the other found a graduated effect over time (Adair et al. 2013; Fall et al. 2008).

**CONCLUSIONS AND RELEVANCE**

Because of low average BWs in LMICs, interventions to increase BW will likely decrease DM risk among these populations, with relatively little effect on risk at the highest end of BW. Focusing on the inverse relationship for BW below 4,000g, (Whincup et al. 2008) estimated that a population-wide intervention that increases BW as little as 100g – with larger increases (up to 200g) in populations with marginal nutrition – could translate into reductions in risk of DM by five to 10 percent. A change of ~100g in BW is not outside the realm of possibility via maternal supplementation, as has been documented by several studies; however, it appears that in Southeast Asia, the low starting weight of infants could reduce the absolute potential for change in BW (Gillespie and Haddad 2003; Abu-Saad and Fraser 2010; Christian 2003).

In other work conducted by SPRING, the three most effective interventions to reduce LBW/increase BW included maternal multiple micronutrient supplementation (MMS), balanced protein energy supplementation, and family planning to increase interpregnancy intervals (Pomeroy et al. 2014). The most effective of these appears to be MMS, which reduces risk of LBW by about 17 percent (when adjusted for the sociodemographic profile of that cohort). In that study, the authors were able to simulate the effects of such a reduction on cardiovascular disease risk later in life, using evidence of linkages throughout the life course.
In the case of DM, it is more difficult to make such estimations of reductions in mortality and morbidity. While it appears that the majority of the studies found a significant inverse relationship between BW (below a certain threshold) and DM risk, variance exists in the nature of the relationship, how persistent it is throughout the life cycle, and what modifies that risk in children and adults (Tinnion et al. 2013). Part of the reason this is a difficult relationship to understand is that DM has a multifactorial and dynamic etiology. This etiology includes strong contributions from childhood and adult body weight trajectory, lifestyle, and genetic factors (Whincup et al. 2008).

Beyond the greater heterogeneity in evidence on the initial effects of BW on DM, this review outlines the uncertainty on the compound DM risk of weight gain and/or high BMI on LBW. To further complicate the issue, this body of evidence also uses IR, dysglycemia, and other pre-DM conditions often in lieu of DM; however, as noted earlier, the pathway from these conditions to DM is not entirely clear.

To estimate risk reduction on adult DM-related mortality due to improved birth outcomes, one would require more concrete information on how modifiable this underlying risk is, by what factors, and when during the lifecycle it is most likely modified. It is also necessary to define clear progression from DM to mortality (preferably among several different demographic groups), as there are multiple routes available with uncertainty related to many of them (Fonseca 2009). Greater use of prospective cohort design rather than reliance on retrospective chart review would also improve estimates of DM risk and improve the discussion around causality.

This review highlights the variety of data on the effects of BW on DM and pre-DM condition risk in later life. While consensus is growing that BW does have a significant effect on DM risk, more work is needed to conclusively define that association in LMICs, in different ethnic groups, and across the spectrum of BW. In the meantime, all efforts to reduce LBW should continue, given its proven relationship with neonatal mortality (Yasmin et al. 2001; Ashworth 1998). The work in this review and elsewhere to improve estimates of the relationship between LBW and later life NCD risk should be considered as additional support for efforts to reduce LBW. The improved estimates will allow for more accurate accounting of the lives saved over the life course by improved birth outcomes.


**Annex**

**Search Terms**

This list is a subset of the larger systematic evidence review conducted for the ELN-NCD Model.

| Birth Outcomes | Pregnancy Outcomes, Birth Outcomes, Low Birthweight, LBW, Low Birth Weight, IUGR, Fetal, Birth Weight, Infant Weight, Size at Birth, Small at Birth, Birthweight *(Done for the larger study but excluded from this review unless study also included analysis of BW outcomes: SGA, Small for Gestational Age; Preterm birth, gestational, Preterm, PTB)* |
| Growth and Metabolism | Growth, Weight Gain, Catch up, Obesity, Fat, Overweight, Adiposity |
| DM | Diabetes, Diabetes Mellitus, Type II Diabetes, Glucose, Insulin, Metabolic Imbalance, Blood Sugar |