Proportion of Type 2 Diabetes Cases Resulting From Impaired Fetal Growth

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OBJECTIVE — During the past decade, several researchers have demonstrated a higher risk of type 2 diabetes in relation to lower birth weight. This theory, referred to as the “thrifty phenotype” hypothesis, posulates that impaired fetal growth predisposes individuals to the development of diabetes and other metabolic abnormalities. This article examines the importance of fetal growth in the etiology of diabetes by estimating the proportion of diabetes cases associated with this exposure.

RESEARCH DESIGN AND METHODS — The importance of an exposure or its correlate as a potential cause of a disease can be assessed by estimating the proportion of cases that could be prevented if the exposure was eliminated from a defined population. This proportion is referred to as the population-attributable fraction (PAF). Published studies of the association between diabetes and birth weight were reviewed and selected for further analysis if data were presented that enabled PAF calculation. In addition, PAFs were calculated for higher birth weight cutoffs because researchers have postulated that the lowest birth weight category may not capture all cases of fetal growth retardation. Studies have shown that exposure classified in this broader manner can produce unbiased PAF estimates, even if many subjects are falsely classified as exposed.

RESULTS — PAFs for the lowest birth weight category ranged from 0.01 to 0.25. In this analysis, PAFs for diabetes did not exceed 0.35. In contrast, >50% of diabetes cases in the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study were attributable to excess adiposity as reflected by a BMI of ≥26 kg/m² (PAF >0.50).

CONCLUSIONS — Impaired fetal growth or its correlates account for a minority (<0.50) of type 2 diabetes cases.

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Much interest has developed during the past decade regarding what is known as the “thrifty phenotype” hypothesis (1–3). This hypothesis proposes that type 2 diabetes and associated conditions such as hypertension and lipid abnormalities result from inadequate intrauterine conditions for optimal fetal growth. Several studies have demonstrated a higher risk of diabetes or impaired glucose tolerance in relation to lower birth weight, including 2 large cohort studies of U.S. health professionals that included thousands of subjects (1,4–8). Critics of these reports focus on the highly selected populations included in several of these studies and the likely presence of residual confounding by correlates of birth weight (9,10). Other investigators have pointed out that low birth weight probably does not causally account for a substantial proportion of diabetes cases because only a relatively small proportion (~10%) of infants fall into this category (6).

Despite these factors, the originators of the thrifty phenotype hypothesis have downplayed an important role for genetic factors in the etiology of type 2 diabetes and recently concluded that “environmental, probably nutritional factors operating in early (fetal and possibly infant) life play a major causative role in NIDDM [type 2 diabetes]” (3). Regarding the issue of a low proportion of exposed diabetes cases, those researchers made the point that low birth weight inaccurately classifies the actual cause, which they postulated to be a currently unidentified “environmental condition” (3). This adverse condition may be present even at higher birth weight categories and may result in the failure of the fetus to reach its optimal birth weight. Hales et al. (3) gave as an example a baby weighing 7.0 lb exposed to an inadequate intrauterine environment who would, under conditions of optimal nutrition, have gone on to reach a birth weight of 9.0 lb (3). I will refer to this theory as fetal underdevelopment syndrome (FUS) in this article. Currently, no methods exist to measure whether suboptimal fetal development has occurred within normal birth weight categories, although the likelihood of this occurrence is probably very low in higher birth weight categories.

A method is available to assess the proportion of cases of a disease resulting from a given exposure that is referred to as the population-attributable fraction (PAF). The PAF reflects the proportion of cases of a disease that could be prevented if the exposure was removed from a given population. Levin (11) first proposed this concept in 1953 and called it “attributable risk” (11), and it has since had other names, including “etiologic fraction” (12) and “population-attributable risk” (13), thus creating the potential for confusion because of the use of different terminology for the same concept. In this article, I assess the importance of both low birth weight and FUS as a cause of type 2 diabetes by calculating PAFs for this exposure in published studies that included the requisite data for these calculations.

RESEARCH DESIGN AND METHODS

I searched Medline from 1991 through April 2000 for all articles written in the
English language that contained the medical subject headings (MeSH) “diabetes mellitus (exploded),” “birth weight,” and “human.” I began the search in 1991 because an important article on the association between birth weight and diabetes risk in adult life first appeared at that time (1). This search yielded a total of 1,383 references, but most of these addressed issues related to immediate pregnancy outcomes in relation to type 1 and gestational diabetes versus the target issue of the effect of birth weight on the risk of diabetes development as an adult. Therefore, the search was restricted further by eliminating references using the Boolean operator “not” that contained the MeSH “diabetes, gestational,” “fetal macrosomia,” or “pregnancy outcome.” These restrictions yielded 123 potential articles for this analysis.

Potential articles had to satisfy the following eligibility criteria: assessment of diabetes as the outcome in adult life and presentation of original data in the publication on diabetes incidence in relation to birth weight that permitted calculation of the PAF. Only 5 studies fulfilled these criteria. Several studies examined glucose as a continuous measure in relation to birth weight (14,15), including 2 studies of prenat al exposure to famine (16,17), but an estimate of PAF cannot be made from this information. Other studies were not included because they considered a combined outcome (either impaired glucose tolerance or diabetes) (1,7) and therefore did not permit estimation of the PAF for the effect of birth weight on diabetes alone.

**Analysis**

The PAF is defined as the excess number of cases resulting from an exposure divided by the total number of cases in a defined population (13). This quantity can be calculated several different ways. If the cumulative incidence in the exposed and unexposed subjects is known along with the number of exposed subjects, then the following yields the excess number of cases resulting from the exposure or a correlate:

\[
\text{Excess cases} = (\text{incidence}_{\text{exposed}} - \text{incidence}_{\text{unexposed}}) \times \text{number}_{\text{exposed}} \tag{1}
\]

Dividing the excess cases by the total number of cases yields the PAF. For example, cumulative incidences of 0.2 in the exposed and 0.1 in the unexposed with 100 exposed and 900 unexposed subjects result in a PAF of \((0.2 - 0.1) \times 100)/(0.2 \times 100 + 0.1 \times 900) = 10/110 = 0.091\).

Algebraic manipulation of Eq. 1 results in a formula for the PAF that depends on the relative risk (RR) of the exposure and the proportion of exposed cases only.

\[
\text{PAF} = \frac{\text{proportion of exposed cases} \times (\text{RR} - 1))}{\text{RR}} \tag{2}
\]

Equation 2 demonstrates several general features of the association among the proportion of exposed cases, RR, and potential importance of the exposure as a cause of a disease in a population. As an example, consider the results of a case-control study of the association between lung cancer and cigarette smoking (18). Smoking was associated with an estimated RR of lung cancer of 52.8, and a high proportion of the 298 cases were exposed (0.983), which led to a PAF of 0.983 \times (52.8/52.8) = 0.964. Therefore, 96% of lung cancer cases would not have occurred during the same time period if no cigarette smoking had occurred in this study population. In general, the PAF increases as the proportion of exposed cases and the RR increase. High levels of the proportion of exposed cases or the RR do not ensure a high PAF. For example, if the RR associated with the exposure is 1.5, and all cases are exposed, then the PAF associated with this combination is 0.33. Similarly, a high RR does not ensure a high PAF. For example, an RR of 100 results in a PAF of only 0.099 when 0.10 of cases are exposed.

Although birth weight is directly measurable, FUS is not because a newborn’s optimal birth weight cannot be known, only the actual birth weight can. In fact, conceiving of any method to measure optimal birth weight and failure to achieve it in humans in the near or distant future is difficult. FUS probably, however, occurs rarely or not at all in higher birth weight categories (e.g., >3,500 g or 7.7 lb). Therefore, capturing all cases of FUS may be possible if the birth weight cutoff is set appropriately high. This would undoubtedly lead to many unexposed subjects falsely included in the exposed category. To be specific, many infants with birth weights between 2,500 and 4,000 g will not have experienced FUS, yet they will be classified as positive for this exposure. This proposed classification scheme would lead to considerable bias in the estimation of RR of diabetes associated with this exposure. Interestingly, studies have shown that setting a wider range for exposure (e.g., higher birth weight) in this manner leads to a more accurate estimate of the true PAF when considerable underascertainment of exposure occurs at a lower cutoff value, even though many truly unexposed subjects will be falsely classified as exposed in the process (19,20). I used this property of the PAF to estimate the potential importance of the FUS as a cause of type 2 diabetes, even though no direct measurement of this exposure is currently possible. This property is especially important because an overly narrow definition of exposure can underestimate the PAF. If a broad exposure definition does not capture all exposed subjects for a factor associated with higher disease risk, then the PAF will be biased toward the null value, although this effect will likely be small unless many truly exposed subjects are classified as unexposed.

I also used the distributive property of the PAF to calculate the PAF for the sum of multiple exposure categories (19). For example, if the diabetes PAF associated with a BMI >30 kg/m² is 0.3 and with a BMI 27–30 kg/m² is 0.2, then the PAF for a BMI ≥27 kg/m² is 0.4. Proof of these properties and further technical information regarding the PAF may be found elsewhere (13,19–22).

**RESULTS**

Type 2 diabetes PAF for low birth weight

Table 1 displays characteristics of the 5 eligible publications regarding birth weight and the incidence of diabetes in adult subjects in which data were presented that permitted PAF calculation. The table numbers in these publications from which data were extracted for PAF calculations are shown in Table 1. Cumulative incidences were calculated from the numerator and denominator data provided. No adjustment could be made for potential confounding factors (except as indicated below) because the results presented in these articles did not typically contain sufficiently stratified data to permit these calculations. In calculating the PAF for low birth weight, the lowest birth weight category presented in each article was compared with the remaining subjects. The crude (unadjusted) results of 2 studies demonstrated a higher diabetes risk in the higher birth weight category, which possibly reflects the presence of gestational diabetes (6,8). For these 2 studies, results were presented with the higher birth weight categories excluded so as not to underestimate the effect of low birth weight on diabetes
Table 1—Characteristics of eligible studies for the estimation of type 2 diabetes PAF in relation to low birth weight compared with all other birth weights except as indicated

<table>
<thead>
<tr>
<th>Study (criteria for diabetes diagnosis)</th>
<th>Subjects (n)</th>
<th>Age (years)</th>
<th>Lowest birth weight category</th>
<th>Proportion of exposed cases</th>
<th>RR</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pima Indians, Table 1 (2-h glucose ≥11.1 mmol/l) (6)</td>
<td>1,147</td>
<td>20–39</td>
<td>&lt;2,500 g</td>
<td>0.06</td>
<td>1.51</td>
<td>0.02*</td>
</tr>
<tr>
<td>Pima Indians, Table 1 (fasting glucose ≥7.8 mmol/l) (6)</td>
<td>1,147</td>
<td>20–39</td>
<td>&lt;2,500 g</td>
<td>0.05</td>
<td>1.37</td>
<td>0.01*</td>
</tr>
<tr>
<td>Nurses’ Health Study, Tables 2 and 3 (self-reported physician diagnosis) (8)</td>
<td>60,244</td>
<td>57.1–60.9†</td>
<td>&lt;5 lb</td>
<td>0.10</td>
<td>1.94</td>
<td>0.05†</td>
</tr>
<tr>
<td>Swedish men, Table 4 (National Diabetes Data Group) (5)</td>
<td>1,093</td>
<td>60†</td>
<td>&lt;3,250 g</td>
<td>0.34</td>
<td>1.99</td>
<td>0.17</td>
</tr>
<tr>
<td>Swedish men, Table 3 (World Health Organization criteria) (26)</td>
<td>2,294</td>
<td>35–56</td>
<td>≤3,000 g</td>
<td>0.34</td>
<td>3.52</td>
<td>0.25</td>
</tr>
<tr>
<td>Male Health Professionals Study, Table 3 (self-reported physician diagnosis) (4)</td>
<td>22,312</td>
<td>48–84</td>
<td>&lt;5.5 lb</td>
<td>0.05</td>
<td>1.77</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Highest birth weight category (≥4,500 g) excluded from this comparison as explained in the text; †higher birth weight categories (>8.5 lb) excluded from this comparison as explained in the text; ‡mean; §subjects with a parental history of diabetes excluded.

Table 2—PAF of diabetes for individual and combined birth weight categories

<table>
<thead>
<tr>
<th>Study population</th>
<th>PAF nonreferent categories combined</th>
<th>PAF for each birth weight category vs. the referent category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pima Indians (6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-h glucose ≥11.1</td>
<td>0.01</td>
<td>2,500–3,499 g</td>
</tr>
<tr>
<td>Fasting glucose ≥7.8</td>
<td>0.03</td>
<td>0.01 Referent</td>
</tr>
<tr>
<td>Nurses’ Health Study, no parental diabetes history (8)</td>
<td>0.27</td>
<td>5.0–5.5 lb</td>
</tr>
<tr>
<td>Swedish men (5)</td>
<td>0.28</td>
<td>1.77</td>
</tr>
<tr>
<td>Swedish men (26)</td>
<td>0.35</td>
<td>0.25</td>
</tr>
<tr>
<td>Male Health Professionals Study (4)</td>
<td>0.07</td>
<td>5.0–5.5 lb</td>
</tr>
</tbody>
</table>

CONCLUSIONS — Low birth weight or its correlates account for only a small to
Because of variability in study design and the absence of statistical methodology, no summary estimate for PAF from these 5 studies is presented. Although the larger sample size of several of these studies would have contributed greater weight to a summary estimate, the larger studies used less valid methods for assessment of diabetes status (self-report). Even if a summary meta-analytic estimate of PAF was available for multiple studies, it would be of questionable validity given these differences in methodology across publications.

Although fetal growth retardation plays a less important role than adiposity in the development of diabetes, it may nonetheless have a substantial effect on the development of diabetes in a given population, although this effect may vary, as seen in this analysis.

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References
2. Hales CN, Barker DJ: Type 2 (non-insulin-