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What’s Known On This Subject

We know from previous studies that IDMs may be at risk of delays affecting motor, cognitive and behavioral development. Results have been inconsistent, limited in age range and small samples have made it difficult to control for confounding factors.

What This Study Adds

This case-control design of 2833 children followed longitudinally shows that (1) expressive language is delayed in IDMs into early childhood, except for children of educated mothers, and (2) affected children appear to have a genetic liability to GD.

ABSTRACT

BACKGROUND. Previous studies have suggested that language is affected in infants of diabetic mothers, yet there have been no systematic investigations to address this question.

OBJECTIVE. Our goal was to compare infants of diabetic mothers and controls on language outcomes from ages 18 months to 7 years.

METHODS. This was a case-control longitudinal design with 2 birth cohorts: 1835 singletons from the Quebec Longitudinal Study of Child Development (born October 1997 to July 1998) and 998 twins from the Quebec Newborn Twin Study (born November 1995 to July 1998). Cases were 221 infants of diabetic mothers (105 singletons and 116 twins), and controls were 2612 children (1730 singletons and 882 twins) for whom at least 1 language measure from ages 18 months to 7 years was available. Exclusion criteria were gestation of $<32$ weeks. The outcome measures were McArthur Communicative Development Inventory expressive and receptive vocabulary and grammar at 18 months and 30 months, the Peabody Picture Vocabulary Test receptive vocabulary at 48 months and expressive and receptive vocabulary at 60 months, and Early Development Instrument teacher-assessed communication at 72 months and 84 months (kindergarten and first grade).

RESULTS. Analyses of variance (controlling for gender, socioeconomic status, and perinatal factors) revealed effects of gestational diabetes on expressive language at 18, 30, and 72/84 months. Infants of diabetic mothers scored 0.27 to 0.41 SD lower than controls and were 2.2 times more at risk of a language impairment. Genes and maternal education both moderated the effect of gestational diabetes on expressive language during this period.

CONCLUSION. Gestational diabetes hinders expressive language in offspring into middle childhood. Genes are strongly associated with the risk of delays in infants of diabetic mothers, and offspring of educated mothers are less affected. Pediatrics 2008;122: e1073–e1079

FROM 2% TO 14% of infants are born to mothers with gestational diabetes (GD),\textsuperscript{1,2} and this rate is on the increase.\textsuperscript{3} Although most infants of diabetic mothers (IDMs) are asymptomatic at birth and seem to develop normally,\textsuperscript{4} studies have shown lower general IQ\textsuperscript{4–6}, lower verbal IQ,\textsuperscript{4,5} and a higher incidence of language,\textsuperscript{5} inattention, and motor delays\textsuperscript{11,12} in IDMs. However, because most studies rely on small samples, time-specific assessments, and fail to control for confounding variables, it remains difficult to assess the impact of GD on neurodevelopment.

This article focuses on language development in IDMs. Using a case-control longitudinal design in 2 large birth cohorts, we tested the hypotheses that (1) GD hinders language development, and (2) it does so longitudinally, after controlling for possible confounds.
IDMs experience high or fluctuating blood glucose during gestation, which causes other metabolite anomalies in late gestation and immediately after birth. Brain structures may be vulnerable to these anomalies in late gestation and early development. One study has shown pups from diabetic mice sustain structural lesions to the hippocampus and impaired recognition memory (RM). RM deficits have been documented by using event-related potentials in human IDMs, at birth, at 6 months, and 8 months. Memory plays an important role in word knowledge consolidation, including short-term and working memory both in visual and auditory modalities, and word knowledge is the basis of grammatical skills, therefore, we examined whether RM could account for language discrepancies in IDMs.

Finally, we tested for moderators of the effect of GD. When moderation occurs, the link between cause and outcome may be difficult to establish. Using genetic modeling, we tested whether genes protect or make some children more vulnerable to the effects of GD. We also tested whether maternal education moderates the effect of GD because language is highly permeable to family environment.

METHODS

Participants

Data come from 2 longitudinal cohort studies of child development: (1) the Quebec Longitudinal Study of Child Development (QLSCD), a demographically and geographically representative cohort of 2133 singletons in the province of Quebec, Canada; and (2) the Quebec Newborn Twin Study (QNTS), which conducted comparable assessments on a population-based sample of 1430 twins (715 families) from the greater Montreal area. Average family income was slightly above the Canadian national average in both samples.

In the QLSCD, subjects were recruited from birth records to constitute a representative sample of families having given birth between October 1997 and July 1998. In the QNTS, all twin births in the greater Montreal area between November 1995 and July 1998 were recruited at delivery. Ethical approval and informed parental consent were obtained before each data collection; non-nominal data only were available for analyses.

To be included, infants had to be born without major medical conditions. Medical charts were available for 3305 infants and their mothers, 2127 singletons and 1182 individual twins. IDMs were 130 singleton (6.1%) and 137 individual twins (12.1%). Exclusion criteria were gestation <32 weeks and average 1/5-minute Apgar score of <6 (n = 66, 6 singletons and 60 twins) and having at least 1 language measure available. This was the case for 1835 (QLSCD) and 998 (QNTS) of the remaining children: 221 IDMs, 105 singletons and 116 individual twins, and 2612 controls, 1730 singletons and 882 individual twins.

Sample sizes vary for specific measures. For the RM measure at 6 months, the first 322 families from the twin population were targeted, with 414 infants corresponding to inclusion criteria, 58 cases and 356 controls. In the QLSCD, 30-month language was assessed in 1037 children only; 956 children corresponding to inclusion criteria, 60 cases and 896 controls. French was the first language for 92% and 85% of the QLSCD and QNTS children, respectively.

Measures

Perinatal data were derived from medical charts. Cases were assigned according to GD diagnosis in medical charts (2-hour glucose tolerance test value in capillary whole blood of at least 7.8 mmol/L between the 22nd and 30th week of gestation). Examiners were blind to the child’s group status, or in the case of parents, unaware that GD would be the basis of group comparisons.

Data on substance abuse (cigarette, alcohol), maternal education, and family income were obtained via self-report from the mothers 6 months after birth. Cigarette and alcohol consumption were dichotomized: (0) no smoking, (1) smoking at least 1 trimester; (0) <1 drink (1) >1 drink per week at least 1 trimester. Maternal education was converted to a 3-point scale (0) no high-school diploma, (1) high school or technical diploma, and (2) university degree. Family income was (0) below poverty level or (1) above poverty level for number of individuals and geographic location.

At 18 months, zygosity was assessed for same-gender twin pairs (n = 237) based on physical resemblance using the Zygosity Questionnaire for Young Twins and confirmed by using a DNA analysis of 8 to 10 highly polymorphous genetic markers on half the sample. Concordance was 94%, which is similar to rates in samples of older twins. On language measures, twins from the same family were assessed by separate examiners; when parental assessments were used, the mother filled out questionnaires regarding 1 twin on 1 occasion and the other twin 2 weeks later.

Preschool Language

Before age 3, language was measured using parent reports on the McArthur Communicative Development Inventory-Short Form (MCDI): expressive and receptive vocabularies using a 77-word checklist at 18 months (QNTS only) and a 100-word checklist at 30 months (QLSCD and QNTS) from which parents indicated words the child says (expressive) and words the child only understands (receptive); receptive grammar at 18 months (QNTS) based on a child’s understanding of 12 simple commands; expressive grammar at 30 months (both samples) using a 3-point scale (0) is unable to combine words, (1) sometimes combines words, and (2) often uses word combinations. The French versions of the MCDI were adaptations of the American short forms. French and English raw means were not significantly different.

At 42 months (QLSCD) and 60 months (QNTS), receptive vocabulary was assessed with French or English versions of the Peabody Picture Vocabulary Test (PPVT). Expressive vocabulary at 60 months (QNTS)

*Children identified as using >1 language (6% of the total sample) were assessed by using the language they use most often based on the parent’s indication.
used an adapted version of the PPVT where children were first asked to name designated objects. There were language-based mean differences on the normative scores for the PPVT but not on the raw scores; therefore, raw scores were retained for analyses.

Both the MCDI and PPVT are widely used and have excellent psychometric properties.26,27

Kindergarten and First-Grade Communication, Reading, and Math
Oral communication (α = .93), reading (α = .81), and math (α = .80) were assessed by teachers via 6 Likert-type items each at midterm in kindergarten and first grade (72–84 months; QNTS) using the Early Development Instrument (EDI).28 The oral communication scale included (1) uses correct grammar, (2) is able to relate a factual event, (3) communicates well with others, (4) articulates clearly, (5) is able to tell a story, (6) is able to communicate his or her needs. To maximize sample size, kindergarten and first-grade scores were averaged allowing 1 missing value.

Cognitive Measures
RM was assessed in a Visual Habituation paradigm29 on a subsample of twins at 6 months. RM was computed as the infant’s reaction to novelty: average time gazing at a novel stimulus (trials 1–2) minus average time gazing at the habituation stimulus in the last 2 habituation trials. RM indicates the extent to which the infant recognizes the novelty phase stimulus as different.30

Block Design of the Weschler Preschool and Primary Scale of Intelligence-Revised was administered at 48 months of age (QLSCD) and 60 months of age (QNTS) as a proxy for Nonverbal IQ (NVIQ),31 because it has the highest subscale–scale correlation of the nonverbal subtests.32 Visually Cued Recall33 was administered at 60 months of age. RM was assessed in a Visual Habituation paradigm on a subsample of twins at 6 months. RM was computed as the novelty phase stimulus as different.30

RESULTS
Tables 1 and 2 compare IDMs and controls on sociodemographic and perinatal data, respectively. Overall, IDMs and controls did not differ at birth as a function of child gender, family income, or marital status of parents. They did differ on mother’s educational attainment, with less-educated mothers being more at risk of GD, and age of the mother at birth, with older mothers being more at risk of GD. There were no significant differences between IDMs and controls on hypoxia and jaundice in offspring, as well as cigarette and alcohol consumption by the mother. Significant differences were found for

### TABLE 1
Comparisons of IDMs and Controls on Sociodemographic Variables

<table>
<thead>
<tr>
<th></th>
<th>IDMs</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QLSCD</td>
<td>QNTS</td>
<td>All</td>
</tr>
<tr>
<td>Total sample, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>105</td>
<td>116</td>
<td>221</td>
</tr>
<tr>
<td>Maternal education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school/technical diploma</td>
<td>24 (23)</td>
<td>33 (28)</td>
<td>57 (26)</td>
</tr>
<tr>
<td>University degree</td>
<td>25 (24)</td>
<td>19 (16)</td>
<td>44 (20)</td>
</tr>
<tr>
<td>Poverty, n (%)</td>
<td>22 (21)</td>
<td>29 (25)</td>
<td>51 (23)</td>
</tr>
<tr>
<td>Single mother, n (%)</td>
<td>3 (3)</td>
<td>7 (6)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>31.23 (5.43)</td>
<td>31.01 (5.10)</td>
<td>31.12 (5.25)</td>
</tr>
</tbody>
</table>

P values are for χ² value on count measures and F value on continuous measures.
previous pregnancies, with mothers being more at risk of GD in later pregnancies, and gestation duration, because IDMs were born half a week earlier than controls. This accounted for slightly lower birth weights and heights, lower Apgar scores, and the longer hospital stay of IDMs. Once gestation was taken into account, IDMs and controls no longer differed. Finally, IDMs had a higher rate of cesarean section, and their mothers were more at risk of gestational hypertension.

**Do IDMs Differ From Controls on Language Outcomes?**

Table 3 reports ANCOVAs comparing IDMs and controls on language outcomes separately for the QLSCD and QNTS.† Models controlled for child gender, gestation duration, birth weight, Apgar score, gestational hypertension, and alcohol/cigarette consumption during pregnancy.

IDMs scored between .27 to .41 SD below controls on expressive vocabulary and expressive grammar at 18 and 30 months once covariates were controlled. This translates into a 4- to 12-word difference in vocabulary on a scale of 77 words (mean: 18 at 18 months) and a difference of up to 10 words on a scale of 100 words (mean: 62 at 30 months). Regarding early expressive grammar, additional analyses were conducted on a sample including only 1 twin per family to avoid an effect of family aggregation. Results were identical to those reported including both twins. Interactions between child gender and GD were tested for all measures and were not significant.

### TABLE 2 Comparisons of IDMs and Controls on Perinatal Variables

<table>
<thead>
<tr>
<th></th>
<th>IDMs</th>
<th>Controls</th>
<th>p</th>
<th>p(\text{Pred} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QLSCD</td>
<td>QNTS</td>
<td>All</td>
<td>QLSCD</td>
</tr>
<tr>
<td>Total sample</td>
<td>105</td>
<td>116</td>
<td>221</td>
<td>1730</td>
</tr>
<tr>
<td>Gravida, mean (SD)</td>
<td>2.17 (1.10)</td>
<td>1.94 (0.90)</td>
<td>2.05 (1.01)</td>
<td>1.78 (0.90)</td>
</tr>
<tr>
<td>Gestation, wk, mean (SD)</td>
<td>38.62 (1.37)</td>
<td>37.58 (2.04)</td>
<td>37.92 (1.65)</td>
<td>39.13 (1.40)</td>
</tr>
<tr>
<td>Birth weight, kg, mean (SD)</td>
<td>3.39 (0.50)</td>
<td>2.52 (0.49)</td>
<td>2.94 (0.66)</td>
<td>3.41 (0.49)</td>
</tr>
<tr>
<td>Height, cm, mean (SD)</td>
<td>50.89 (2.67)</td>
<td>47.11 (2.90)</td>
<td>48.96 (3.36)</td>
<td>50.98 (2.59)</td>
</tr>
<tr>
<td>Apgar, mean (SD)</td>
<td>8.84 (0.91)</td>
<td>8.73 (0.87)</td>
<td>8.78 (0.89)</td>
<td>8.99 (0.72)</td>
</tr>
<tr>
<td>Days in hospital, mean (SD)</td>
<td>2.91 (1.46)</td>
<td>7.61 (6.99)</td>
<td>5.33 (5.62)</td>
<td>2.83 (1.76)</td>
</tr>
<tr>
<td>Cesarean section, mean (SD)</td>
<td>13 (12)</td>
<td>70 (60)</td>
<td>83 (37.6)</td>
<td>268 (16)</td>
</tr>
<tr>
<td>Hypoxia, frequency (%)</td>
<td>6 (5.7)</td>
<td>NA</td>
<td>NA</td>
<td>121 (7)</td>
</tr>
<tr>
<td>Hypoglycemia, frequency (%)</td>
<td>1 (1)</td>
<td>NA</td>
<td>NA</td>
<td>25 (1.4)</td>
</tr>
<tr>
<td>Polycythemia, frequency (%)</td>
<td>0 (0)</td>
<td>NA</td>
<td>NA</td>
<td>7 (0.4)</td>
</tr>
<tr>
<td>Jaundice, frequency (%)</td>
<td>22 (21)</td>
<td>NA</td>
<td>NA</td>
<td>302 (17.5)</td>
</tr>
<tr>
<td>Hypertension, frequency (%)</td>
<td>6 (5.7)</td>
<td>22 (19)</td>
<td>28 (12.7)</td>
<td>34 (2)</td>
</tr>
<tr>
<td>Alcohol (&gt;1/wk), frequency (%)</td>
<td>2 (1.9)</td>
<td>5 (4.3)</td>
<td>7 (3.2)</td>
<td>60 (3.5)</td>
</tr>
<tr>
<td>Smoker, frequency (%)</td>
<td>27 (25.7)</td>
<td>34 (29.3)</td>
<td>61 (27.6)</td>
<td>448 (16)</td>
</tr>
</tbody>
</table>

NA indicates not available. P values are for \(\chi^2\) value on count measures and F value on continuous measures:

- after control for gestation,
- after control for age of mother at birth, and
- excluding twin pregnancies.

*Assessed in child.

Table 3 ANCOVAs for Language Measures in the LSCDQ and QNTS

<table>
<thead>
<tr>
<th>Age, mo</th>
<th>Measures</th>
<th>Sample</th>
<th>n</th>
<th>IDMs, Mean (SD)</th>
<th>Controls, Mean (SD)</th>
<th>F Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>18a</td>
<td>Expressive vocabulary</td>
<td>QNTS</td>
<td>861</td>
<td>−0.25 (0.96)</td>
<td>0.02 (0.99)</td>
<td>6.12</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Receptive vocabulary</td>
<td>QNTS</td>
<td>861</td>
<td>−0.06 (1.00)</td>
<td>0.00 (0.99)</td>
<td>0.38</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>Receptive grammar</td>
<td>QNTS</td>
<td>861</td>
<td>−0.10 (1.16)</td>
<td>0.02 (0.98)</td>
<td>0.56</td>
<td>0.46</td>
</tr>
<tr>
<td>30a</td>
<td>Expressive vocabulary</td>
<td>LSCDQ</td>
<td>955</td>
<td>−0.28 (1.09)</td>
<td>0.02 (0.99)</td>
<td>4.74</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Receptive vocabulary</td>
<td>LSCDQ</td>
<td>955</td>
<td>−0.18 (1.10)</td>
<td>0.01 (0.98)</td>
<td>2.19</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>Expressive grammar</td>
<td>LSCDQ</td>
<td>955</td>
<td>−0.38 (1.21)</td>
<td>0.03 (0.97)</td>
<td>8.46</td>
<td>0.003</td>
</tr>
<tr>
<td>30b</td>
<td>Expressive vocabulary</td>
<td>QNTS</td>
<td>764</td>
<td>−0.33 (1.22)</td>
<td>0.04 (0.96)</td>
<td>5.73</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Expressive grammar</td>
<td>QNTS</td>
<td>764</td>
<td>−0.28 (1.18)</td>
<td>0.04 (0.96)</td>
<td>4.28</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Receptive grammar</td>
<td>QNTS</td>
<td>764</td>
<td>0.04 (0.97)</td>
<td>0.01 (1.01)</td>
<td>1.32</td>
<td>0.25</td>
</tr>
<tr>
<td>42b</td>
<td>Receptive vocabulary</td>
<td>LSCDQ</td>
<td>1728</td>
<td>−0.16 (0.81)</td>
<td>0.02 (1.00)</td>
<td>2.75</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>Expressive vocabulary</td>
<td>QNTS</td>
<td>721</td>
<td>−0.12 (0.90)</td>
<td>0.04 (0.99)</td>
<td>0.47</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>Receptive vocabulary</td>
<td>QNTS</td>
<td>721</td>
<td>−0.09 (0.86)</td>
<td>0.01 (1.01)</td>
<td>0.62</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>Oral communication</td>
<td>QNTS</td>
<td>833</td>
<td>−0.30 (1.21)</td>
<td>0.05 (0.96)</td>
<td>4.66</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Reading</td>
<td>QNTS</td>
<td>833</td>
<td>−0.04 (0.96)</td>
<td>0.03 (0.99)</td>
<td>0.39</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Math</td>
<td>QNTS</td>
<td>833</td>
<td>−0.10 (1.02)</td>
<td>0.05 (0.93)</td>
<td>1.28</td>
<td>0.26</td>
</tr>
</tbody>
</table>

All scores were corrected for gestational age rounded in months and standardized. All models controlled for child gender, gestation duration, birth weight, average Apgar score, gestational hypertension, and alcohol/cigarette consumption during pregnancy.

- MCDI.
- PPVT.
- EDI.
87% of controls were using word combinations often by 30 months compared with 74% of IDMs.

At 42 and 60 months, there were no differences between IDMs and controls on expressive and receptive vocabulary. On the 72/84 months EDI Oral Communication Scale (QNTS), IDMs performed .35 SD below controls. The groups did not differ on EDI reading and math.

Table 4 compares GD effect sizes on MCDI Expressive Vocabulary and Grammar and EDI Oral Communication with effect sizes of other predictors. Although effect sizes for GD are modest, they are second only to child gender, mother’s education, and family income.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Expressive Vocabulary at 18 mo, QNTS (n = 861)</th>
<th>Expressive Vocabulary at 30 mo (n = 1720)</th>
<th>Expressive Grammar at 30 mo (n = 1720)</th>
<th>Communication at 72/84 mo, QNTS (n = 833)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F</td>
<td>P</td>
<td>η</td>
<td>F</td>
</tr>
<tr>
<td>GD</td>
<td>6.23</td>
<td>.01</td>
<td>.008</td>
<td>7.48</td>
</tr>
<tr>
<td>Income</td>
<td>3.57</td>
<td>.06</td>
<td>NS</td>
<td>24.00</td>
</tr>
<tr>
<td>Maternal education</td>
<td>48.66</td>
<td>&lt;.001</td>
<td>.028</td>
<td>6.68</td>
</tr>
<tr>
<td>Gender</td>
<td>9.10</td>
<td>.003</td>
<td>.012</td>
<td>11.95</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.07</td>
<td>.79</td>
<td>NS</td>
<td>4.31</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.50</td>
<td>.48</td>
<td>NS</td>
<td>4.72</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>0.45</td>
<td>.50</td>
<td>NS</td>
<td>13.06</td>
</tr>
<tr>
<td>Age (mother)</td>
<td>0.00</td>
<td>.99</td>
<td>NS</td>
<td>4.28</td>
</tr>
<tr>
<td>Gestation</td>
<td>0.51</td>
<td>.48</td>
<td>NS</td>
<td>0.06</td>
</tr>
<tr>
<td>Birth weightb</td>
<td>2.78</td>
<td>.09</td>
<td>NS</td>
<td>0.46</td>
</tr>
<tr>
<td>Apgar scorea</td>
<td>0.04</td>
<td>.85</td>
<td>NS</td>
<td>2.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.05</td>
<td>.82</td>
<td>NS</td>
<td>0.33</td>
</tr>
</tbody>
</table>

a Pooled QLSCD and QNTS samples.  

Do Genes and Maternal Education Moderate the Effect of GD?
Genetic models were fitted to the ELC (n = 994: 181 MZ pairs, 38 IDMs and 324 controls, and 316 DZ pairs, 66 IDMs and 566 controls) specifying (1) similar genetic contributions to variations on the ELC for IDMs and controls and (2) different genetic contributions for IDMs and controls. The model specifying different genetic parameters for IDMs and controls offered a better fit to the data (χ² = 2.5, P = .93; AIC = -11.5; RMSEA = .008) than the model constraining genetic parameters to be equal across groups (χ² = 26.13, P = .002; AIC = -8.13; RMSEA = .13) indicating that genes do moderate the effect of GD on expressive language. Figure 1 illustrates genetic and environmental contributions to variations on the ELC in IDMs and controls. Additive genetic ac-
count for 93% (95% CI: .89–.95) of the variance on the ELC in IDMs, whereas they account for a mere 41% (95% CI: .30–.53) in controls. This indicates that genetic factors are strongly associated with the vulnerability of IDMs to expressive language delays.

To test whether maternal education moderates the effect of GD, the significance of an interaction term (maternal education × GD) was tested to predict the ELC (n = 1865) with the same controls used previously. Maternal education does moderate the effect of GD on ELC (F3,1711 = 3.502, P = .03). As Fig 2 illustrates, IDMs of mothers without a high school diploma fared significantly worse than controls (F1,276 = 10.679, P = .001), whereas differences between IDMs and controls of mothers with a high school or technical diploma (F1,941 = 3.50, P = .55) or a University degree (F1,478 = 1.308, P = .25) were not significant.

DISCUSSION
This study is the first, to our knowledge, to show that GD hinders expressive language development in offspring. On all but 1 expressive language measure between 18 and 84 months, IDMs performed .27 to .41 SD below controls and were 2 times more at risk of a language impairment. Perinatal, sociodemographic data, and nonverbal cognitive skills could not account for this discrepancy, and GD effect sizes, although modest, are second only to gender, poverty, and maternal education. Thus, we conclude that GD is associated with a persistent deficit in expressive language evident into middle childhood. The fact that expressive language is specifically affected is noteworthy given previously documented motor delays in IDMs and the higher motor demands of language production compared with language comprehension.

This study also identifies 2 potent moderators of the effect of GD on language development: genes and maternal educational.

How Do Genes Matter?
Genetic modeling revealed that additive genes moderate the effect of GD on expressive language: protection or vulnerability genes are thus strongly associated with IDMs’ expressive language skills. However, what these genes are or do remains speculative. The genetic protection/vulnerability to GD continuum may operate at multiple levels. At the neurodevelopment level, the brains of some IDMs may be more vulnerable to insults of omissions (iron and oxygen depletion caused by the cascading effects of fluctuating blood-glucose levels) or commissions (vulnerability of the blood–brain barrier shortly after birth to neurotoxic agents, such as bilirubin). The specific brain structures vulnerable to these need to be identified. At a more systemic level, any of the systems dealing with the increased demands induced by GD (eg, increasing fetal insulin and red blood cell production, providing sufficient iron supplies to developing brain cells) may be more or less efficient. At a more functional level, similar brain insults may have heterogeneous effects on language development depending on how other brain structures take over (plasticity) or compensate through other skills. Until we know which mechanisms are operating and which brain structures are affected, it remains difficult to isolate the specific genetic factors involved.

Maternal Education: Is the Effect of GD on Language Reversible?
Offspring of more educated mothers seemed spared, suggesting that protective environmental factors, such as the more stimulating environments provided by educated mothers, may diminish the initial impact of GD on language. However, a note of caution is needed: the moderating effect of maternal education may simply reflect the moderating effect of genes. Experimental studies are needed to test whether stimulation through parental support or surrogate maternal care can limit the effects of GD on language outcomes.

LIMITS AND CONCLUSIONS
In all probability, these mothers were given state-of-the-art care regarding GD management, which is available without cost in Quebec. However, because the studies were not conducted to assess GD management, data on treatment and the relative severity of GD were unavailable. Future studies should assess whether deleterious effects appear at lower levels of glucose intolerance in mothers to determine what is safe for offspring brain development.

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REFERENCES

Gestational Diabetes Hinders Language Development in Offspring
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Pediatrics 2008;122:e1073-e1079
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