Cognitive function in children and subsequent type 2 diabetes mellitus

Gunilla M Olsson¹, PhD
Anna-Lena Hulting², Professor
Scott M Montgomery³, Docent

¹ Neuroscience, Uppsala University, Uppsala; and Public Health, Örebro University, Örebro, Sweden.
² Endocrinology, Metabolism and Diabetes, Karolinska University Hospital, Stockholm, Sweden
³ Clinical Epidemiology Unit, Karolinska University Hospital, Stockholm; and Clinical Research Centre, Örebro University Hospital, Örebro, Sweden; and Primary Care and Social Medicine, Imperial College, London, UK

Running title: Cognitive function and type 2 diabetes mellitus

Correspondence:
Dr. Gunilla Maria Olsson
Uppsala University
Neuroscience/Pharmacology,
BMC, Box 593
SE-751 24 Uppsala, Sweden
gunilla.olsson@neuro.uu.se

Received for publication 19 July 2007 and accepted in revised form 7 December 2007.
ABSTRACT

**Objective:** To assess if a diagnosis of type 2 diabetes mellitus (T2DM) by age 42 years is associated with prior cognitive deficits in childhood.

**Research Design and Methods:** Logistic regression estimated T2DM risk among 9,113 members of the 1958 British birth cohort; the National Child Development Study (NCDS). Associations with T2DM were estimated for general ability and reading comprehension assessments at age 11 years, modelled using standard deviation units. Adjustment was for markers of early-life exposures; social and material family characteristics; sex; and disability; with further adjustment for BMI at age 7 years.

**Results:** Adjusted odds ratios (with 95% CI) for T2DM (n=69) are 0.67 (0.51 to 0.87) for general ability and 0.58 (0.44 to 0.77) for reading comprehension. Neither additional adjustment for BMI, nor limiting the definition of T2DM to onset after age 33 years, altered the associations substantially.

**Conclusions:** Impaired cognitive function may precede clinical onset of T2DM.
Type 2 diabetes mellitus (T2DM) is associated with decreased cognitive function in adults (1,2) particularly among elderly people (3). Less is known about cognitive function in children who will subsequently receive a diagnosis of T2DM in adulthood. We investigated the association of cognitive function at age 11 years with a subsequent T2DM diagnosis using British longitudinal data.

**RESEARCH DESIGN AND METHODS**

The National Child Development Study is following all those born between 3rd-9th March 1958 (approximately 17,000 births) and living in Great Britain (4). At birth, midwives recorded information on: sex, birth weight, gestational age, mother’s age, her age at leaving school, smoking during pregnancy (after the 4th month) and the Registrar General’s social class based on occupation (5). All significant diagnoses, impairments, disabilities, height and weight were recorded at the medical examination conducted at age seven years. Diabetes in a first-degree relative was recorded at this time. Cognitive function was assessed at age 11 years with tests administered at school for general ability (comprising verbal and non-verbal components) with a range of 0-79 (6) and reading comprehension with a range of 0-35 (7). A medical examination and record review at age 16 years recorded confirmed or possible diagnoses of DM. Interviews at ages 33 and 42 years identified T2DM through a question about ‘diabetes that did not require insulin injections’ and excluding diabetes only present during pregnancy (4). Ethnic origin was recorded at age 42 years.

Despite some attrition the cohort remains generally representative, with 11,419 subjects participating at age 42 years (4). Those with a confirmed or suspected diagnosis of DM (type 1 or 2) by age 16 years, as well as those with T1DM or insufficient information on DM, were excluded from all analyses. Those with missing data for the main measures were also excluded, so information for 9,182 subjects was available for analysis.

A diagnosis of T2DM after age 16 years was the dependent variable in logistic regression analysis. The general ability and reading comprehension test scores were examined separately and modelled using standard deviation units (Z-scores). Adjustment was for sex, birth weight, gestational age (a separate category identified 853 without a valid value), parental social class, maternal smoking during pregnancy, age mother left school, mother’s age at delivery, presence of mild or severe mental retardation, disability and ethnic origin (97% White British): Potential confounding factors were modelled as categorical variables, except birth weight. Separate models were adjusted for BMI (available for a subset of subjects) at age seven years, modelled as a continuous variable. Further models examined T2DM diagnosed after age 33 years.

**RESULTS**

Cohort members with a diagnosis of T2DM after age 16 years had statistically significant lower assessment scores at age 11 years after adjustment for potential confounding factors (table 1). The associations reflect a general shift in distribution, rather than because of a small number of outlying values. The odds ratios indicate the reduction in risk of later T2DM associated with one standard deviation increase in test score. Adjustment for BMI in childhood did not eliminate the significant association of lower test scores with increased T2DM risk. Exclusion of subjects with DM with onset prior to age 33 years reduced the sample size with valid data, but lower test scores at age 11 years were still significantly associated with increased T2DM risk. The associations were not notably altered by exclusion of cohort members with a first degree relative with DM, or by modelling gestational age in days as a continuous variable, or birth weight as a categorical variable (data not shown).
CONCLUSIONS

Poorer cognitive function at age 11 years was associated with an increased risk of T2DM by age 42 years. Although ‘DM that does not require insulin injections’ is a somewhat imprecise definition of T2DM, we minimised the risk of confounding by other forms of DM by excluding all cohort members with a diagnosis of any form of DM by age 16 years (as well as those with insufficient information). The association of poorer childhood cognitive function with T2DM with onset after age 33 years provides further evidence that this finding is not confounded by other forms of DM and that there may be a long delay between impaired cognition in childhood and symptomatic onset of T2DM.

There was relatively little impact of multiple simultaneous adjustment for indicators of in utero exposures including those associated with T2DM risk (5), conventional markers of cultural and material circumstances in childhood, mental or physical diagnoses in childhood and ethnic origin. Even though it may be intermediate in the causal pathway and thus an over-adjustment, including BMI at age seven years (prior to the pubertal growth spurt) in the models did not eliminate the association of childhood cognitive function with subsequent T2DM. Residual confounding is always possible, but the relatively small impact of adjustment for well-recognised indicators of early life exposures and childhood conditions is consistent with a more direct association between childhood cognitive function and subsequent T2DM. Further adjustment for BMI at age seven years provided additional control for relevant lifestyle factors and obesity risk.

It is possible that cognitive deficits present in childhood influence lifestyle factors that increase the risk of T2DM. Alternatively, poorer glycaemic control or other shared risk factors may influence both cognitive development and the risk of T2DM. Insulin resistance is proposed as a possible mediator between dietary intake and cognitive deficits and there is some evidence of altered β-cell function preceding the development of clinical hyperglycaemia (8,9). Chronically elevated blood glucose levels have been linked to decreased cerebral blood flow in T2DM and animal models suggest that myelin production is impeded by high blood glucose levels (10). It is possible that such mechanisms, even prior to overt clinical hypoglycaemia, could impair cognitive development in childhood thus helping to explain the lower levels of cognitive function in T2DM patients and greater susceptibility to risks for cognitive decline. This suggests that very early detection of sub-clinical disease and treatment may be of value in protecting against cognitive deficits.

ACKNOWLEDGEMENTS

The funding for this project was obtained through British Economic and Social Research Council grant L326253061 that forms part of the Capability and Resilience Network. GMO and ALHs participation was funded by AFA.
REFERENCES

TABLE 1. Test scores at age 11 years and the risk of subsequent type 2 diabetes mellitus diagnosed between ages 16 and 42 years

<table>
<thead>
<tr>
<th>Cohort members without a diagnosis of DM by age 16 years</th>
<th>Subjects without T2DM N=9,113</th>
<th>Subjects with T2DM N=69</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ability</td>
<td>Mean, (SD)</td>
<td>Mean, (SD)</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td></td>
<td>45, (16)</td>
<td>37, (17)</td>
<td>0.63 (0.49 to 0.79)</td>
<td>0.67 (0.51 to 0.87)</td>
</tr>
<tr>
<td>Reading comprehension</td>
<td>17, (6)</td>
<td>13, (6)</td>
<td>0.56 (0.44 to 0.72)</td>
<td>0.58 (0.44 to 0.76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort members without a diagnosis of DM by age 16 years and with information on BMI at age 7 years</th>
<th>Subjects without T2DM N=7,701</th>
<th>Subjects with T2DM N=59</th>
<th>Unadjusted</th>
<th>Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ability</td>
<td>Mean, (SD)</td>
<td>Mean, (SD)</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td></td>
<td>45, (15)</td>
<td>39, (18)</td>
<td>0.66 (0.51 to 0.85)</td>
<td>0.70 (0.53 to 0.93)</td>
</tr>
<tr>
<td>Reading comprehension</td>
<td>17, (6)</td>
<td>13, (7)</td>
<td>0.58 (0.45 to 0.76)</td>
<td>0.60 (0.44 to 0.80)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cohort members without a diagnosis of DM by age 33 years</th>
<th>Subjects without T2DM N=7,878</th>
<th>Subjects with T2DM N=48</th>
<th>Unadjusted</th>
<th>Adjusted†</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ability</td>
<td>Mean, (SD)</td>
<td>Mean, (SD)</td>
<td>OR* (95% CI)</td>
<td>OR* (95% CI)</td>
</tr>
<tr>
<td></td>
<td>45, (15)</td>
<td>37, (18)</td>
<td>0.61 (0.46 to 0.81)</td>
<td>0.68 (0.50 to 0.93)</td>
</tr>
<tr>
<td>Reading comprehension</td>
<td>17, (6)</td>
<td>14, (7)</td>
<td>0.58 (0.43 to 0.78)</td>
<td>0.63 (0.45 to 0.86)</td>
</tr>
</tbody>
</table>

* Odds ratios (OR) calculated using logistic regression estimate the risk of subsequent T2DM for each standard deviation change in test score.
† Adjustment is for sex, mental retardation (mild or severe), disability, family social class at birth (seven categories), birth weight in ounces, gestational age (less than 35 weeks, 35 to 36 weeks, 37 to 42 weeks, over 42 weeks and gestational age unavailable), ethnic origin (White British, Irish, White other, White and Black Caribbean, White and Black African, White and Asian, other mixed race, Indian, other Asian, Caribbean, African, other Black, other ethnic group), smoking during pregnancy, age mother left school and her age at delivery.
‡ Adjustment is as for †, but also for BMI at age seven years.