Association of Insulin-like Growth Factor I and Insulin-like Growth Factor–Binding Protein-3 With Intelligence Quotient Among 8- to 9-Year-Old Children in the Avon Longitudinal Study of Parents and Children

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ABSTRACT. *Background.* **Insulin-like growth factor I (IGF-I) is a hormone that mediates the effects of growth hormone and plays a critical role in somatic growth regulation and organ development. It is hypothesized that it also plays a key role in human brain development. Previous studies have investigated the association of low IGF-I levels attributable to growth hormone receptor deficiency with intelligence but produced mixed results. We are aware of no studies that investigated the association of IGF-I levels with IQ in population samples of normal children.**

Objectives. **To investigate the association of circulating levels of IGF-I and its principle binding protein, IGF-binding protein-3 (IGFBP-3), in childhood with subsequent measures of IQ.**

Methods. **The cohort study was based on data for 547 white singleton boys and girls, members of the Avon Longitudinal Study of Parents and Children, with IGF-I and IGFBP-3 measurements (obtained at a mean age of 8.0 years) and IQ measured with the Wechsler Intelligence Scale for Children (at a mean age of 8.7 years). We also investigated associations with measures of speech and language based on the Wechsler Objective Reading Dimensions test (measured at an age of 7.5 years) and the Wechsler Objective Language Dimensions test (listening comprehension subtest only, measured at an age of 8.7 years). For some children (n = 407), IGF-I (but not IGFBP-3) levels had been measured at ~5 years of age in a previous study. Linear regression models were used to investigate associations of the IGF-I system with the measures of cognitive function.**

Results. **Three hundred one boys and 246 girls were included in the sample. IGF-I levels (mean ± SD) were 142.6 ± 53.9 ng/mL for boys and 154.4 ± 51.6 ng/mL for girls. IQ scores (mean ± SD) were 106.05 ± 16.6 and 105.27 ± 15.6 for boys and girls, respectively. IGF-I levels were associated positively with intelligence. For every 100 ng/mL increase in IGF-I, IQ increased by 3.18 points (95% confidence interval [CI]: 0.52 to 5.84 points). These positive associations were seen in relation to the verbal component (coefficient: 4.27; 95% CI: 1.62 to 6.92), rather than the performance component (coefficient: 1.06; 95% CI: −1.67 to 3.78), of IQ. There was no evidence that associations with overall IQ differed between boys and girls. In a data set with complete information on confounders (n = 484), controlling for birth weight (adjusted for gestation), breastfeeding, and BMI slightly strengthened the associations of IGF-I levels with IQ. Additionally controlling for maternal education and IGFBP-3 levels attenuated the associations (change in IQ for every 100 ng/mL increase in IGF-I levels: 2.51 points; 95% CI: −0.42 to 5.44 points). The weakening of associations in models controlling for markers of parental socioeconomic position and education could reflect shared influences of parental IGF levels on parents' own educational attainment and their offspring's IGF-I levels. In unadjusted models examining associations of Wechsler Objective Reading Dimensions and Wechsler Objective Language Dimensions test scores with IGF-I levels, there was no strong evidence that performance on either of these tests was associated with circulating IGF-I levels, although positive associations were seen with both measures. Associations between IGF-I levels measured at age 5 and Wechsler Intelligence Scale for Children scores (n = 407) were similar to those for IGF-I levels measured at age 7 to 8. For every 100 ng/mL increase in IGF-I levels at 5 years of age, IQ increased by 2.3 points (95% CI: −0.21 to 4.89 points).**

Conclusions. **This study provides some preliminary evidence that IGF-I is associated with brain development in childhood. Additional longitudinal research is required to clarify the role of IGF-I in neurodevelopment. Because IGF-I levels are modifiable through diet and other environmental exposures, this may be one pathway through which the childhood environment may influence neurodevelopment.** *Pediatrics* **2005;116:e681–e686. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-2390; *insulin-like growth factor, IQ, neurodevelopment, cohort study.***

ABBREVIATIONS. ALSPAC, Avon Longitudinal Study of Parents and Children; CI, confidence interval; GH, growth hormone; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor–binding protein; WISC, Wechsler Intelligence Scale for Children; WOLD, Wechsler Objective Language Dimensions; WORD, Wechsler Objective Reading Dimensions.

Poor fetal and postnatal growth is associated with impaired neurodevelopment. Infants with low birth weights experience delays in reaching motor milestones and have low IQs. These patterns are seen across the range of birth weights and do not seem to be attributable to socioeconomic confounding.[1,2] Similarly, short stature, which is a mea-

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sure of poor postnatal growth and nutrition, is associated with low scores in tests of cognitive function and poor educational achievement.[3,4]

Biological mechanisms linking poor growth and impaired neurodevelopment are not known. One possible pathway is through the growth hormone (GH)/insulin-like growth factor (IGF)-I system. IGFs mediate the effects of GH on tissues and play a key role in somatic growth regulation and organ development in childhood.[5] Animal studies suggest that IGF-I also plays an important part in brain development, with roles ranging from neuroprotection after neuronal damage to neurogenesis, myelination, synaptogenesis, and dendritic branching.[6–8] It has therefore been hypothesized that IGF-I may mediate the associations of fetal growth with adult IQ.[2] In support of this hypothesis, mice with transgenic overexpression of IGF-I have increased brain size,[9] whereas mice with a targeted IGF-I gene deletion have reduced brain size.[10] Among elderly human subjects, studies found that those with higher levels of IGF-I performed better on tests of cognitive function and had lower rates of cognitive decline.[11] Previous studies investigated the association of low IGF-I levels attributable to GH receptor deficiency with intelligence among children with this rare genetic defect, with mixed results.[12–14] Furthermore, a recent study reported that small-for-gestational age children treated with GH showed improvements not only in growth but also in IQ.[15] To the best of our knowledge, no studies to date have investigated the association of IGFs with measures of intellectual performance in population samples of normal children. The aim of this study was to investigate the association between circulating levels of IGF-I and its main binding protein, IGF-binding protein-3 (IGFBP-3), measured at ~8 years of age and IQ.

METHODS

Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a geographically based, cohort study investigating factors influencing the health, growth, and development of children. All pregnant women residing within a defined part of the former county of Avon, in southwest England, with an expected date of delivery between April 1991 and December 1992 were eligible. A total of 14 541 pregnancies were enrolled (~85% of those invited), 13 617 of which resulted in singleton offspring surviving to 12 months of age; additional details have been published previously.[16,17]

Ethical approval was obtained from the study's own ethics committee and local research ethics committees. Data in ALSPAC are collected through self-completion of postal questionnaires, abstraction from medical records, and examination of the children at research clinics.

The children forming the basis of this analysis were the 547 white singleton children with both a stored blood sample and a measure of intellectual performance, obtained at ages of ~8 years and ~9 years, respectively. Nonwhite children and those with missing ethnicity data (n = 32) were excluded because preliminary analyses suggested that their IGF levels differed from those of white children. Because the number of such children was small, separate investigation of associations for this group was not conducted.

IGF-I and IGFBP-3 Measurements

Blood samples were taken from children at either the 7-year focus clinics or a second clinic (the "Before Breakfast Study") approximately 6 to 12 months later. The mean age at the time of blood sampling was 8.0 years (range: 6.9–8.5 years). Serum levels of IGF-I were determined with a radioimmunoassay using a monoclonal antibody (Blood Products, Elstree, Hertfordshire, United Kingdom) and recombinant peptide (Pharmacia, Stockholm, Sweden) for standard and tracer, after iodination with the chloramine-T method. Samples were analyzed after acid/acetone extraction to remove the IGFBPs, with an excess of IGF-II added to the extract to saturate any residual IGFBPs.[18] Serum levels of IGFBP-3 were determined with a radioimmunoassay using an in-house polyclonal antibody raised against recombinant nonglycosylated IGFBP-3. The assay was calibrated with recombinant glycosylated IGFBP-3 (obtained from Dr C. Maack, Celitrix, Santa Clara, CA). The average coefficients of variation for intraassay variability for IGF-I and IGFBP-3 were 6.7% and 3.6%, respectively, and those for interassay variation were 12% and 14%. IGF-I levels, IGFBP-3 levels, and IGF-I/IGFBP-3 ratios were all adjusted for age with the residuals method. For some children in ALSPAC (n = 407), IGF-I levels (but not IGFBP-3 levels) had been measured at ~5 years of age in a previous study.[19]

Measures of Intellectual Performance and Neurodevelopment

Our primary outcome measure was the Wechsler Intelligence Scale for Children (WISC)-III (United Kingdom version) measure of cognitive ability (IQ), assessed at a mean age of 8.7 years.[20] Measures of IQ were recorded a mean of 0.7 years (range: 0–2.0 years) after blood samples were obtained. The WISC-III is the current version of the most widely used test of neurocognitive ability. A short form of the measure was used in which alternate items (always starting with item 1 on the standard form) were used for all 10 subtests, with the exception of the coding subtest, which was administered in its full form. Scores were age standardized according to the authors' guidelines. In a secondary analysis, we also investigated associations with measures of speech and language based on the Wechsler Objective Reading Dimensions (WORD) test[21] and the Wechsler Objective Language Dimensions (WOLD) test[22] (listening comprehension subtest only). The WISC-III and WOLD test scores were obtained from the focus clinic held at 8.5 years of age (mean: 8.7 years; range: 7.5–9.4 years), and the WORD test scores were measured at clinics held when the children were 7.5 years of age (mean: 7.5 years; range: 6.9–8.0 years).

Possible Confounding or Mediating Variables

We assessed the effect on IGF-I-IQ associations of controlling for the following variables: (1) the child's birth weight, adjusted for gestational age with the residuals method; (2) breastfeeding, reported by the mothers in postnatal questionnaires and categorized into 5 groups (ie, exclusive breastfeeding for a minimum of 3 months, exclusive breastfeeding for up to 2 months, exclusive breastfeeding for up to 1 month, nonexclusive breastfeeding, or never breastfed); (3) the child's BMI, calculated from the height and weight measurements taken at the clinic visit when the child was 7 years of age; (4) mother's highest educational attainment, measured at 32 weeks of gestation and categorized into 3 levels (less than O level, O level, or more than O level) on the basis of self-report (O ["ordinary"] levels are tests of academic performance in a range of core curriculum subjects [eg, mathematics, English, science, history, and geography, with 1 O level per subject area] taken by schoolchildren at the age of ~16 years, the minimum age at which children leave school in England; children with qualifications higher than O levels often proceed to attend a university, and those who do not obtain any O level certifications do not continue in the school system and enter the labor market or proceed to vocational training courses); (5) housing tenure, measured at ~8 weeks of gestation and classified into 3 groups (ie, mortgaged/owned, council rented, or rented/other); this provides an indication of parental affluence, because richer parents are more likely to own/mortgage their houses, rather than living in rented accommodations; (6) the child's social class, measured at 32 weeks of gestation, based on the highest occupational level of the 2 parents, and categorized as nonmanual or manual (where manual occupation signifies lower socioeconomic position); and (7) the child's milk, dairy product, and protein intakes, measured at 7 to 8 years of age with a 3-day food diary. We also assessed associations of the child's IGF-I levels with the educational level of

the partner of the child's mother, as reported by the mother and categorized as described above.

Statistical Methods

Linear regression models were used to investigate the association of measures of the IGF system with cognitive function among male and female subjects separately and both genders combined, controlling for gender. In addition to assessing associations with IGF-I and IGFBP-3 levels, we assessed associations with the IGF-I/IGFBP-3 ratio. IGFBP-3 binds 80% to 90% of IGF-I in the circulation; therefore, the IGF-I/IGFBP-3 ratio has been used as a crude indicator of available (unbound) IGF-I.

Preliminary analyses were performed for the subset with both IGF and IQ data available (n = 547). To assess confounding, additional models were fitted on the basis of those with complete data for all confounders (see above; n = 484). The first model adjusted only for the age at which IQ was measured and gender (for analyses including both boys and girls) (model A). The next model controlled for birth weight adjusted for gestational age, breastfeeding, and BMI (model B). Previous analyses of ALSPAC data found associations of birth weight and growth with IGF-I levels,[19] and other analyses suggested that birth weight and breastfeeding may influence IQ; controlling for these factors therefore assessed whether IGF-I was a possible mediator of these associations or confounded them. We then assessed the possible confounding effect of mother's education, a measure of socioeconomic position (model C). In separate models (not shown), we assessed possible socioeconomic confounding by assessing the effect of controlling for housing tenure and social class. In our final model, we assessed whether associations of IGF-I levels with IQ were strengthened when we crudely assessed associations with unbound (bioavailable) IGF-I levels by controlling for IGFBP-3 levels in the models (model D). We also investigated the interaction between gender and IGF-I levels in the initial model and the possible confounding effect on associations with IGF-I levels of the education of the mother's partner and the child's consumption of dairy products/milk/protein. These latter components of the diet are the factors associated most strongly with IGF-I levels in other studies and may confound or mediate any association with IGF-I levels.[23] In a secondary analysis, we assessed the association of IGF-I levels measured at 5 years of age with IQ measured at 8 to 9 years of age. All analyses were conducted with Stata 8 software (Stata Corp, College Station, TX).

RESULTS

Characteristics of Subjects

The characteristics of the children included in this analysis are given in Table 1. Girls had higher levels of both IGF-I and IGFBP-3. Those with a missing IQ measure tended to have somewhat lower levels of IGF-I (145.2 vs 147.9 ng/mL) and IGFBP-3 (4493 vs 4949 ng/mL) (data not shown). Compared with the whole cohort, subjects with measures of IGF-I and intellectual performance tended to come from more affluent socioeconomic backgrounds (86.2% vs 80.3% were from nonmanual social class backgrounds) and were more likely to have been breastfed (85.9% vs 75.9%). IQ levels among the 547 children included in this analysis were slightly higher than those of other cohort members. Among those included in this analysis, mean IQ scores were 106.1 and 105.3 for boys and girls, respectively. Among the remaining ALSPAC study members, mean IQ scores were 104.9 and 104.6 for boys and girls, respectively.

Association of IGF and IQ

Among the 547 subjects with measures of IQ and IGF-I, there was a positive association between IGF-I levels and IQ scores (Table 2). For every 100 ng/mL increase in IGF-I level, IQ increased by 3.18 points (95% confidence interval [CI]: 0.52 to 5.84 points). This association was stronger for girls than for boys, although this difference must be interpreted with caution because there was no statistical evidence of an interaction between gender and IGF-I levels with respect to their association with IQ (P = .49 for interaction). There was no evidence of an association between IQ and IGFBP-3 levels or IGF-I/IGFBP-3 ratios. In a separate analysis (not shown), we found

TABLE 1. Characteristics of Study Members

	Boys (n = 301)	Girls (n = 246)
Continuous variables (mean ± SD)		
Age at IGF measurement, y	7.96 ± 0.37	7.96 ± 0.34
IGF-1, ng/mL	142.6 ± 53.9	154.4 ± 51.6
IGFBP-3, ng/mL	4820 ± 1690	5106 ± 1734
IQ	106.05 ± 16.6	105.27 ± 15.6
BMI, kg/m^2	16.1 ± 1.9	16.4 ± 2.4
Birth weight adjusted for gestational age, g	3599 ± 441	3512 ± 406
Categorical variables, no. (%)		
Mothers education (n = 300/246)		
Less than O level	47 (15.7)	49 (19.9)
O level	122 (40.7)	86 (35.0)
More than O level	131 (43.7)	111 (45.1)
Housing tenure (n = 299/246)		
Mortgage/owned	256 (85.6)	205 (83.3)
Council rented	21 (7.0)	19 (7.7)
Rented/other	22 (7.4)	22 (8.9)
Social class (n = 283/233)		
Nonmanual	245 (86.6)	200 (85.8)
Manual	38 (13.4)	33 (14.2)
Breastfeeding (n = 283/235)		
Exclusive breastfeeding	89 (31.4)	94 (40.0)
Exclusive breastfeeding to end of second month	50 (17.7)	32 (13.6)
Exclusive breastfeeding to end of first month	24 (8.5)	28 (11.9)
Nonexclusive breastfeeding	84 (29.7)	44 (18.7)
Never breastfed	36 (12.7)	37 (15.7)

Where data were incomplete for a variable, the number of subjects (male/female) with complete data is given after the description of the variable.

TABLE 2. Association of IGF-I Levels, IGFBP-3 Levels, and IGF-I/IGFBP-3 Ratios With IQ in the ALSPAC Study

	n	Coefficient	95% CI	*P* Value
IGF-I				
Total	547	3.18	0.52 to 5.84	.019
Boys	301	2.32	−1.36 to 5.99	.216
Girls	246	4.24	0.37 to 8.10	.032
IGFBP-3				
Total	547	0.52	−0.42 to 1.45	.277
Boys	301	0.60	−0.70 to 1.91	.364
Girls	246	0.51	−0.82 to 1.83	.451
IGF-I/IGFBP-3 ratio				
Total	547	12.22	−11.27 to 35.72	.307
Boys	301	5.81	−25.69 to 37.32	.717
Girls	246	19.29	−16.41 to 54.99	.288

The coefficient is the change in IQ per 100 ng/mL change in IGF-I level, per 1000 ng/mL change in IGFBP-3 level, or per 1-unit change in IGF-I/IGFBP-3 ratio.

that the IGF-I association was restricted to the verbal component of IQ (coefficient: 4.27; 95% CI: 1.62 to 6.92; $P = .002$), rather than the performance component (coefficient: 1.06; 95% CI: −1.67 to 3.78; $P = .45$). In a sensitivity analysis including the 32 children who were nonwhite or whose ethnicity was unknown, the associations were weakened slightly; for every 100 ng/mL increase in IGF-I level, IQ increased by 2.98 points (95% CI: 0.39 to 5.58 points; $P = .024$).

We assessed the effects on the IGF-I-IQ associations of controlling for a range of possible confounding factors (Table 3). This analysis was restricted to the 484 subjects with complete data on all confounders; therefore, the simple associations (model A) differed somewhat from those reported in Table 2. Controlling for birth weight (adjusted for gestation), breastfeeding, and BMI (model B) strengthened slightly the associations of IGF-I levels with IQ. In addition, controlling for maternal education (model C) and IGFBP-3 levels (model D) attenuated the associations considerably. In additional models (not shown) controlling for 2 other measures of socioeconomic position (housing tenure and social class), associations were weakened more (coefficient for male and female subjects combined: 2.03; 95% CI: −0.87 to 4.94; $P = .17$).

Of note, the educational levels of mothers and their partners were associated with offspring IGF-I levels. Mothers with less than O level, O level, and more than O level education had offspring with mean IGF-I levels of 145 ng/mL (95% CI: 135 to 155 ng/mL), 147 ng/mL (95% CI: 140 to 154 ng/mL), and 153 ng/mL (95% CI: 147 to 160 ng/mL), respectively ($P = .14$ for trend). In relation to the same categories of education for the mothers' partners, offspring mean IGF-I levels were 141 ng/mL (95% CI: 132 to 149 ng/mL), 144 ng/mL (95% CI: 136 to 153 ng/mL), and 156 ng/mL (95% CI: 150 to 162 ng/mL) ($P = .006$ for trend), respectively.

For the subgroup of subjects ($n = 414$) with data on diet, IQ, and IGF-I levels, the possible confounding effect of milk, dairy product, and protein intakes was assessed. In this restricted data set, there was no strong evidence of confounding by dietary intake.

TABLE 3. Multivariate Models Assessing the Effect on IGF-I-IQ Associations of Controlling for Birth Weight, Breastfeeding, BMI, Maternal Education, and IGFBP-3 Levels

	Model A			Model B			Model C			Model D		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
Total ($n = 484$)	2.93	0.12 to 5.73	.041	3.17	0.33 to 6.02	.029	2.63	−0.11 to 5.37	.060	2.51	−0.42 to 5.44	.093
Boys ($n = 262$)	1.88	−2.00 to 5.75	.341	2.18	−1.89 to 6.25	.293	2.07	−1.93 to 6.06	.309	1.89	−2.38 to 6.17	.385
Girls ($n = 222$)	4.20	0.12 to 8.28	.044	4.50	0.33 to 8.67	.035	3.62	−0.28 to 7.51	.069	3.56	−0.61 to 7.74	.094

Model A is a simple model, with no adjustments; model B, model A plus the child's birth weight adjusted for gestation, breastfeeding, and BMI; model C, model B plus maternal education; model D, model C plus IGFBP-3. The coefficient is the change in IQ per 100 ng/mL change in IGF-I level.

Associations With Other Measures of Reading and Language Development

In separate analyses (not shown), we assessed associations with WOLD listening comprehension subtest and WORD test scores. In unadjusted models examining associations for both genders combined ($n = 547$), there was no strong evidence ($P = .11$ and $P = .72$, respectively) that performance on either of these tests was associated with circulating IGF-I levels, although positive associations with both measures were observed. Furthermore, there was evidence of a strong positive association of IGF-I levels with WOLD test scores for girls ($P = .007$), although no association was seen for boys ($P = .90$).

Associations With IGF-I Levels at Age 5

Associations between IGF-I levels at age 5 and WISC-III scores ($n = 407$) were similar to those for IGF-I levels measured at age 7 to 8. For every 100 ng/mL increase in the IGF-I level at 5 years of age, IQ increased by 2.3 points (95% CI: −0.21 to 4.89 points; $P = .07$). Associations were similar for boys (2.6 points; 95% CI: −1.3 to 6.6 points) and girls (2.0 points; 95% CI: −1.3 to 5.4 points) and were with the verbal component ($P = .02$), rather than the performance component ($P = .60$), of IQ.

DISCUSSION

We found that IGF-I levels measured at age 7 to 8 were associated positively with intelligence measured, on average, 0.7 years later. For every 100 ng/mL increase in IGF-I level, IQ score increased by ~3 points (95% CI: 0.52 to 5.84 points). This increase is equivalent to approximately one third of the range of values within IQ score categories, those scoring 110 to 119 in IQ tests are said to be of "high average intelligence," those with scores of 120 to 129 of "high intelligence," and those with scores of 80 to 89 of "low average intelligence." We found no consistent evidence of an association of IGF-I levels with our other measures of neurodevelopment (WOLD and WORD test results). Associations were similar among ALSPAC study members whose IGF-I levels were measured at age 5.

This association of IGF-I levels with IQ was attenuated in models controlling for measures of parental socioeconomic position and education. If IGF-I truly influences childhood neurodevelopment and IQ, then this confounding effect of parental socioeconomic position should be interpreted with caution. Parental education and socioeconomic position are likely to be associated both with their IQ and, through genetic and shared environmental pathways, with their offspring's intelligence. Similarly, offspring IGF-I levels are likely to be associated with parental IGF-I levels, through shared genetic influences.[24] Therefore, rather than confounding the associations of IGF-I levels with IQ, parental education and socioeconomic position may lie on a causal pathway linking IGF-I with IQ. We assessed the effect of controlling for aspects of childhood diet, BMI, and birth weight, all of which influence IGF-I levels,[19,23] and found no evidence of confounding. As with the confounding effects of measures of socioeconomic position, any such confounding requires careful interpretation, because these factors may lie on causal pathways between these exposures and IQ.

The main strengths of this analysis are the detailed assessments of IQ and other measures of cognitive development for cohort members with stored blood samples. Furthermore, the rich, prospectively collected information on a range of other exposures, including the diet and growth of study members and their parents' education and socioeconomic position, allowed assessment of possible confounding factors. A limitation is that IGF-I levels were available for only a subset of study members, who tended to come from more socially advantaged backgrounds than did cohort members who did not have the required data on IQ and IGF-I levels (selection bias). This would bias the IGF-I-IQ associations only if the relationship differed among study members who did not take part in the 7-year clinics; we think this is unlikely to be the case.

The association of IGF-I levels with IQ was restricted to the verbal component of WISC-III. There was only a weak positive association with the performance component. These differences may be chance findings attributable to the small sample size and require replication in larger studies.

Our findings support the hypothesis that IGF-I plays an important role in human brain development and may underlie the associations of birth weight and height with IQ.[1,2,4,25] Additional support for this association comes from a recent study in which 74 small-for-gestational age children were treated with GH and monitored for >2 years. GH therapy (which acts through increasing IGF-I levels) led not only to improved growth but also to improvements in IQ.[15] The association of IGF-I with IQ among children complements the finding that IGF-I is associated with better intellectual performance and with slower rates of cognitive decline in old age.[11,26,27] Additional prospective studies, with serial measurements of IGF-I levels and IQ, are required to clarify the causal association of IGF-I with neurodevelopment and neurodegeneration.

Studies of individuals with genetic conditions associated with very low levels of IGF-I provide a conflicting picture of the role of IGF-I in intelligence. Mental retardation was found in a cohort of Israeli subjects with inherited GH insensitivity.[12] In contrast, no effect on tests of intelligence were reported for a similarly affected cohort of Ecuadorians.[13,14]

Indirect evidence of a role for IGFs in neurodevelopment comes from studies investigating associations of cognitive function with mortality rates. A series of recent studies reported that high childhood IQ is associated with a reduction in overall mortality rates, with an increased risk of some cancers but a reduced risk of heart disease.[28–30] Other prospective studies, using stored blood samples obtained many years before disease onset, found that higher levels of IGF-I are associated with an increased risk of cancer[31] but a reduced risk of heart disease.[32] The similarity of the intelligence-disease and IGF-I-disease associations points to a common pathway and

possibly to a common role for IGF-I in IQ and disease risk.

It has been hypothesized that perturbations of the GH/IGF-I axis may be one mechanistic pathway through which fetal growth restriction influences an individual's risk of developing schizophrenia.[33,34] Of note, measures of poor intellectual performance are related strongly to an individual's risk of schizophrenia.[35,36] The association between IGF-I and IQ presented here provides some evidence in support of a possible role for IGF-I in the pathogenesis of schizophrenia.

Additional studies are needed to replicate these findings and to explore more fully possible causal pathways and confounding factors. Such studies might usefully include analyses of intergenerational influences of IGF-I on education and IQ.

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