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Eighty Five Years of Paediatric Research in the North East Of Scotland – A Partnership between Children, Teachers and Researchers

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Eighty Five Years of Paediatric Research in the North East Of Scotland – Partnership between Children, Teachers and Researchers

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Abstract

There are many common and incurable conditions diagnosed in the elderly, such as dementia and chronic obstructive pulmonary disease (COPD). Understanding the earliest signs of these conditions may lead to early interventions aimed at prevention or cure. A challenge to studying the relationship between childhood factors diseases of the elderly is being able to follow up individuals over the life-course. This review describes a series of cohorts of children attending schools in Aberdeen since the mid-1930s have been followed up and where measurements made in childhood have been related to cognitive and respiratory outcomes in later life. Low birth weight combined with premature delivery are associated with low cognition scores during childhood and this persists to the sixth decade. Childhood asthma and non-asthmatic wheezing symptoms were associated with abnormal breathing tests which persists to the seventh decade and is associated with increased risk of COPD. Deprivation in early life is associated with relatively poor cognitive ability in childhood and adulthood but not with childhood asthma. Together, these findings demonstrate that conditions traditionally considered to affect the elderly are potentially detectable in childhood. What remains to be determined is what might be done in early life to prevent or lessen the burden of disease after retirement.

Keywords: Asthma, Child; Cognitive Development; Longitudinal Studies; School

Introduction

As the average age of our population becomes older, common chronic and incurable conditions (collectively termed non-communicable diseases, NCD) are ever-increasing causes of morbidity and mortality. Dementia, chronic obstructive pulmonary disease (COPD), cancer, coronary artery disease and stroke are all examples of NCD. Although these NCDs often first manifest in the fifth and sixth decades of life, many are thought to have origins in early life. For example reduced birth weight is a risk factor for coronary artery disease (Barker, Winter, Osmond, Margetts, & Simmonds, 1989) and also for the reduced lung function seen in COPD (Barker et al., 1991). Major challenges to associating early life factors to NCD in later life include recording of early life factors and then following up individuals over two or three generations. However, if these considerable challenges can be overcome, then important insight can be gained into the early origins of NCDs, and this might open the way to intervene in order to prevent or lessen their impact on later mortality and morbidity.

Here we describe two clinical settings (neurological and respiratory) where researchers working with Aberdeen schools since 1932 have described the antecedents of decline in cognitive abilities and the decline in lung function and COPD. Collectively dementia (characterised by cognitive decline) and COPD are common and therefore important conditions, and were responsible for 20% of all deaths registered in Scotland in 2015 (NRS Registration Data, 2015). The past collaboration between children, school and research staff is proving an invaluable investment of time and is yielding unique insights into the very early origins of conditions highly relevant to today's society.

Aberdeen Birth Cohort of 1921 and Aberdeen Birth Cohort of 1936

On 1st June 1932, 87,498 children born in Scotland in 1921 had an in-school assessment of "mental ability" called the Moray House Test. The same test was later taken across Scotland on 4th June 1947 by all children born in 1936. The children attending Aberdeen schools who participated in these two tests have been called the Aberdeen Birth Cohorts of 1921 and 1936 (ABC 1921 and ABC 1936). The tests were completed with the support and supervision of teaching staff. No other nation has tested the intelligence of its entire population at the same time and then repeated this 15 years later. At a later stage, researchers were able to link the assessment results from these school children, who were born many years before the NHS, have been linked to health outcomes in the 21st century and childhood intelligence has proved to be a key determinant of mental function and cognitive decline in later life.

As an individual ages there is evidence that maximum "mental ability" or cognitive ability attained (which can be assessed, for example, by measures of literacy) is one of the main determinants of cognitive ability in later life and of survival in general (Whalley & Deary, 2001). A major determinant of life-time cognitive ability is childhood cognition, which itself has been affected by exposure to stimulation, nutrition, and stress in early-life. Based on ABC1921 and ABC1936, childhood intelligence at age 11 has been identified as a strong predictor of cognitive ability in late-life (Chapko et al., 2016; Salarirad et al., 2011; Whalley et al., 2000). Also, recent work performed within ABC1936

supports the idea that children from disadvantaged backgrounds do not achieve the brain's full developmental potential leading to impaired cognition and acquire more dementia-related brain disease, the most common of which is Alzheimer's pathology. Staff et al. demonstrated a significant association between childhood socioeconomic status (SES) and volumes of certain parts of the brain (hippocampi) that are central to learning and memory (Staff et al., 2012). In this study, SES was defined as the combined measure of self-reported paternal occupation, the number of public rooms in the family home and the number of people expected to share the sanitation facility at age 11. Older adults without dementia with low SES in childhood had smaller hippocampi independently of other life-course variables such as cognitive ability at age 11 years, adult SES, gender, and education. This is consistent with the established neurodevelopmental findings that early-life conditions have an effect on structural brain development (Noble et al., 2015) and this remains detectable more than 50 years later. A second study indicated that early life socioeconomic disadvantage defined as paternal occupation at age 11 is associated with increased brain imaging evidence of brain lesions (cerebrovascular disease) in late-life, with its established negative consequences for cognition, stroke, dementia and survival (Murray, McNeil, Salarirad, Whalley, & Staff, 2014).

Since the ABC have demonstrated associations between cognitive abilities and socio-economic circumstances at age 11 and brain ageing (Chapko et al., 2016; Salarirad et al., 2011; Whalley et al., 2000), currently supported by new evidence (Walhovd et al., 2016), the Aberdeen team next looked at which characteristics at birth were linked to childhood intelligence (Deary, 2010). The Aberdeen Children of the 1950s (ACONF) were used to explore the relationship between early life characteristics (i.e. birth weight and gestational age treated as markers for suboptimal conditions in-utero) and cognitive outcomes over the life-course.

Aberdeen Children of the 1950s

The Aberdeen Children of the 1950s cohort (ACONF) is the result of another collaboration between teaching staff and researchers with a focus on children and consists of 12,150 children who were born in Aberdeen between 1950 and 1956 (Batty et al., 2004). As children, all participated in the Aberdeen Child Development Survey (ACDS) (1962-64) conducted on 14,939 primary school children in Aberdeen in 1962 (ages 5–12 years). Participants underwent intelligence quotient (IQ) tests and physical examination in primary schools on three occasions. Childhood cognitive ability was tested within six months of the child's 7th (Moray House Picture Intelligence), 9th (Schonell & Adams Essential Intelligence Test Form) and 11th (Moray House verbal reasoning tests I/II, Moray House English and Moray House Arithmetic) birthdays. The test results of 12,150 children could be linked with the obstetric data stored by the Aberdeen Maternity and Neonatal Databank (AMND) established by Dugald Baird in 1948. In 2001, ACDS participants were asked to complete a postal questionnaire survey, and 63% responded.

Generation Scotland subsample of Aberdeen Children of the 1950s (ACONF-GS)

A subset of ACONF participants, aged 54 – 61 years, was recruited in 2010-2011 as the Aberdeen sample for Generation Scotland: Scottish Family Health Study (GS: SFHS). GS: SFHS is a family-based Scotland-wide study of genetic health and common diseases, with DNA, socio-demographic, and clinical data collected between 2006 and 2011 from 24,000 volunteers aged 18–98 years (Smith et al., 2013). This was a targeted recruitment of ~570 ACONF participants with their family members into GS: SFHS. As part of GS: SFHS, detailed cognitive, clinical and laboratory phenotyping in mid-life was carried out, further enriching existing ACONF data with cognitive measures in mid-life.

In 2013, virtual record linkage follow-up was successfully performed for a subset of ACONF participants who were recruited into GS: SFHS to obtain the full picture of their life-time characteristics. This process was facilitated by the Grampian Data Save Haven (DaSH) at the University of Aberdeen. As a result, 558 individuals were successfully linked (240 men, 318 women; mean age=57.4) and comprised the GS subsample of ACONF (ACONF-GS). This way, the extensive ACONF early-life information supplemented by follow-up information collected around 1999 was combined with detailed mid-life phenotyping as part of GS: SFHS.

The ACONF cohort now allowed the researchers to look at how prenatal, perinatal, and early-life factors (i.e. birth weight, gestation and parental socioeconomic status) and childhood intelligence at seven, nine and 11 years were linked to cognitive ability in the sixth decade of life. In mid-life, tests assessing four domains of cognitive functions were administered: (a) executive functions [Verbal Fluency (VF)]; (b) vocabulary [The Mill Hill Vocabulary scale (MH)], (c) verbal declarative memory [Wechsler Logical Memory test (LM)] and (d) processing speed [Wechsler Digit Symbol substitution task (DS)]. Maximum life-time cognition was estimated with The Mill Hill vocabulary scale (MH). Having described the methods used for the ACONF and ACONF-GS, the next section present the results.

Birth weight, gestational age, and cognitive functions over the life-course in ACONF-GS

There were many findings arising from the ACONF-AMND linkage and these have been divided into four broad areas:

First, we found that those with low birth weight or born pre-term performed significantly worse on intelligence tests compared to the normal group at ages seven or nine. Importantly, the negative effects of low birth weight and pre-term delivery on childhood cognitive abilities reappeared in mid-life. Those with low birth weight or born pre-term performed worse on fluid intelligence tests when compared to the normal group (Tables 1 and 2).

Second, infants at the highest risk of poor cognitive outcomes i.e. the concurrent low-birth weight & preterm infants were the most disadvantaged and had the lowest cognitive scores in mid-life. Those with high birth weight had low cognitive scores at ages seven or nine but this difference has resolved

by age 11 and was not apparent in mid-life. Those born post-term did not differ significantly from those born at term on cognitive functions from childhood to mid-life. In a systematic literature review, Shenkin et al. concluded that there appears to be a small and positive relationship between birth weight and childhood cognitive ability within normal birth weight and term deliveries (Shenkin et al., 2004). Within the normal population of 1946 Birth Cohort, Richards et al. showed that higher birth weight was associated with higher cognitive scores through childhood and early adulthood, followed by a decrease in cognitive score at the highest birthweight category (4.01-5.00 kg). However, the effect was weaker in mid-life, potentially due to adult environmental influences such as educational and occupational attainment (Richards et al., 2001).

Third, this analysis also indicates that certain areas of mental function in later life are differentially affected by poor growth in-utero. Cognitive capacities (e.g. logical thinking, speed of thought and problem solving ability). are sensitive to ageing processes (Deary et al., 2010) and we found a significant association between birth weight and gestational age with Digit Symbol substitution test which is a reliable measure of how quickly information is processed. The test is largely independent of participants' education level and self-reported health status and performance of this test declines with age (Staff, Chapko, Hogan, & Whalley, 2016). However, birth weight and gestational age were not associated with Verbal Fluency test, which is a measure of the brain's capacity to consciously control our thoughts and actions to plan and execute goals. Potentially, this means that only certain aspects of fluid abilities are affected by poor growth in-utero.

Fourth we found that those with low birth weight and/or born pre-term performed significantly worse on childhood intelligence tests compared to the normal group at ages seven or nine. The negative effects of low birth weight and/or pre-term delivery on cognitive functions at ages seven or nine reappeared in mid-life. Those with low birth weight and/or born pre-term performed worse on the mid-life fluid cognitive functions when compared to the normal group. The concurrent low-birth weight & preterm infants were the most disadvantaged with respect to cognitive functions across the life-course. This, overall, further emphasizes the importance of healthy pregnancy and identifies individual differences that may have health and cognitive consequences in later life. Therefore efforts to reduce cognitive impairment in older adults should be informed by a life-course approach with special attention to early-life environment.

Respiratory outcomes

In 1964, the Medical Research Council (MRC) established a research centre in Aberdeen to study many aspects of education including the impact of health on learning. The focus of the research centre was determinants of educational outcomes, and again there was partnership between teaching staff and researchers. Although asthma data was collected to study its impact on educational outcomes, this inadvertently proved to be one of the first surveys of childhood asthma in the world. In the 1960s, childhood asthma was an infrequently studied condition but was becoming notable by its rising prevalence. The researchers asked about lifetime history of asthma, eczema and hayfever of

children aged 9-11 years (P5-7 in Scotland). All children attending schools in the boundaries of Aberdeen city returned a questionnaire that was handed out in class. In 1964 it was considered acceptable for schools to provide researchers with class lists which included names and addresses so that researchers could (and did) visit the homes of non-respondents where questionnaires were completed on the door step. This methodology ensured that participation reached very close to 100%; a small minority of participants declined to take part. This approach is clearly unacceptable in today's society and ethics committees ensure that researchers only receive participant details with their express consent. There have been two outcomes following the MRC team's endeavours in 1964: first, the Aberdeen School Asthma Surveys (ASAS); and secondly what Happens Eventually to Asthmatic children: Sociologically and Epidemiologically cohort (WHEASE).

Aberdeen School Asthma Surveys

Using the same methodology applied in 1964 (Dawson, Illsley, Horobin, & Mitchell, 1969), researchers have tracked the rise and fall of asthma prevalence in primary school children on six further occasions over the next 50 years. Each of these surveys has only been possible with the assistance of school staff who worked in partnership with researchers. In 1964 4% of 9-11 year olds had ever had an asthma diagnosis and this proportion rose to 29% in 2004 before falling to 14% in 2014 (Barnish, Tagiyeva, Devereux, Aucott, & Turner, 2015). There is no other place where childhood asthma prevalence has been followed up over a longer period than in Aberdeen. The ASAS was not originally designed to understand why asthma prevalence has fluctuated so considerably over the years, but the results from the 17,439 questionnaires returned in the seven surveys have been analysed in order to gain insight into what might be important to changing asthma prevalence (Barnish, Tagiyeva, Devereux, Aucott, & Turner, 2017). In this analysis, the relationship between asthma and eczema became slightly stronger over the 50 years of the ASAS (increasing by approximately 7%) and one possible reason for this is that diagnosing asthma became more accurate over time; there is a well-recognised relationship between asthma and eczema and as asthma is more reliably diagnosed the relationship will become stronger. A second notable finding was that the relationship between asthma and parental smoking also became stronger by roughly 7% during a period when parental smoking prevalence halved from 60% to 30%. One possible explanation for the modest increased risk for a child with asthma having a parent who smoked, was that over time children's susceptibility to second hand smoke exposure has increased.

WHEASE Cohort

In the course of the 1964 study, the medical records of a random 20% of the whole study population were reviewed and 121 children were identified as having asthma and a further 167 with wheezy bronchitis. Wheezy bronchitis is a diagnosis not used currently, similar to a rather vague term "viral induced wheeze" used today, but best described as a condition of the airways where wheezing symptoms are only brought on by viral respiratory infections, e.g. the common cold. Unusually, but fortuitously, the 288 children with asthma and wheezy bronchitis were examined by a doctor and had breathing tests done. There was no relationship between childhood asthma status and

socioeconomic status, in contrast to the childhood cognitive outcomes in the ABCs and ACONF. The WHEASE cohort comprises the children with asthma symptoms and a random 5% of the children without asthma symptoms (the “controls”).

When assessed in 1989, during their fourth decade of life, those with childhood asthma and wheezy bronchitis were more likely to have asthma as adults compared to the controls, although the burden of symptoms was greatest for those with childhood asthma (Godden et al., 1994). Lung function testing was also reduced among those who had had asthma and wheezy bronchitis as children; even those individuals whose childhood asthma symptoms had apparently resolved were approximately three times more likely to have abnormal breathing tests than controls.

The next assessment of the WHEASE cohort took place in 2001 when the average age of participants was 48 years (Edwards, Osman, Godden, & Douglas, 2003). At this time, two thirds of the childhood asthma and one third of the childhood wheezy bronchitis group had ongoing asthma symptoms and one in five of the childhood control group has developed adult onset asthma. Lung function was reduced by approximately 10% in the childhood asthma group compared to the childhood control group and the normal age-related decline in lung function was greater in the childhood asthma group. Although the wheezy bronchitis group did not have reduced lung function relative to the childhood control group, they nonetheless had a more rapid decline in lung function. These findings were all independent of smoking, gender and socioeconomic status.

The most recent follow up of the WHEASE cohort was completed in 2014, on the fiftieth anniversary of the original MRC study (Tagiyeva, Devereux, Fielding, Turner, & Douglas, 2016). There were 330 participants followed up in their seventh decade, at least 14 of the original WHEASE cohort had died by this time. More than half of the individuals with asthma as eleven year olds back in 1964 were still reporting asthma symptoms and 80% had a current diagnosis of asthma. The reduction in lung function among those with asthma as primary school children persisted at the 2014 follow up. The persistence of asthma symptoms and reduced lung function confirms earlier reports, but what was new in the 2014 follow up was that a diagnosis of COPD was sought for the first time; COPD becomes more common after the age of 60 so was not previously sought. The prevalence of COPD (as defined by lung function testing) was approximately four times higher in the childhood asthma group and 50% higher in the wheezy bronchitis group in comparison to the control group. Previous to the WHEASE study, wheezy bronchitis was considered a benign condition with no long term consequences but previous research had not followed up the children with “transient wheeze” for long enough.

The WHEASE cohort is the first whole-population based study to demonstrate a link between childhood asthma, wheeze and COPD. The mechanisms leading to asthma and COPD have generally been considered independent, with the “British hypothesis” proposing that that asthma and COPD are different conditions in contrast to the Dutch hypothesis which argues that asthma and

COPD have a common origin. Ironically, it is a British cohort which seems to suggest that the Dutch were right all along.

Early origins of cognitive decline and COPD – the same but different

There are findings of the ABC, ACONF and WHEASE cohorts which are comparable, whilst others offer a conflicting perspective. The primary consistent finding was that lower values of cognitive and lung function testing in primary school children were associated with accelerated decline in cognitive and lung function which was clinically apparent as lower cognition and COPD in later life. There are at least two striking contrasting findings. First, there is clear socioeconomic gradient for cognitive function with children from affluent communities performing better than those from deprived communities but this gradient was not apparent for respiratory function or asthma. Second, whereas diagnosed asthma by 11 years was associated with a persistent reduction in lung function, the reduced cognitive functions seen at seven and nine among the low birth weight and prematurely born individuals were not present at age 11 before being detected in later life, although this association might have been missed due to the measurement error. Children are often said to “grow out of” conditions such as asthma but the evidence from WHEASE suggest otherwise and the findings from ACONF suggest that whilst some reduced measurements may apparently “normalise”, with extended follow up they deficits appear. To say that someone has “grown out of” their illness requires follow up well beyond childhood.

Looking ahead to research in partnership with schools

Schools have always embraced research, after all research is a form of education, but research in the next 50 years will be very different to the last 50. The participation rate in the initial ASAS approached 100%, but the advent of the data protection act and increasing “research fatigue” lead to the 2014 return approaching a disappointing 30%. Future research is likely to involve linkage of routinely acquired data in the health and education systems, and this raises new concerns, including using data given without consent; confounding by different health seeking behaviour between families; not detecting mild conditions where a GP may not be consulted; the practical issue of linking data from the same individual in two complex IT systems and the presence of missing or incorrect data. Governance and methodologies are in place to facilitate linkage of “big data” and so perhaps the future will involve team work between researchers, data custodians and IT departments; we will miss meeting the children themselves.

Table 1. The effects of birth weight on cognitive functions across the life-course

| Cognition | LBW (BW < 2.49 kg) | | | | HBW (BW ≥ 4.08 kg) | | | | | | | | | | | |
|--------------------|--------------------|--------|-----|----------|--------------------|--------|-----|----------|----|--------|------|-------|----|--------|------|-------|
| | Unadjusted | | | Adjusted | Unadjusted | | | Adjusted | | | | | | | | |
| Childhood | N | Coeff. | SE | P | N | Coeff. | SE | P | N | Coeff. | SE | P | N | Coeff. | SE | P |
| CIQ age 7 (n=431) | 14 | | 3.9 | 0.00 | 14 | | 3.7 | | 32 | | | | 32 | | | |
| | | -13.12 | 2 | 1 | | -11.48 | 4 | 0.002 | | -5.82 | 2.65 | 0.028 | | -6.01 | 2.52 | 0.018 |
| CIQ age 9 (n=428) | 15 | | 4.0 | 0.05 | 15 | | 3.9 | | 32 | | | | 32 | | | |
| | | -7.88 | 5 | 2 | | -6.55 | 7 | 0.099 | | -8.13 | 2.83 | 0.004 | | -8.12 | 2.77 | 0.003 |
| CIQ age 11 (n=364) | 14 | | 2.9 | 0.43 | 14 | | 2.9 | | 30 | | | | 30 | | | |
| | | -2.32 | 3 | 0 | | -1.87 | 5 | 0.526 | | -0.73 | 2.05 | 0.722 | | -0.94 | 2.06 | 0.649 |
| Mid-life | | Coeff. | SE | P | | Coeff. | SE | P | | Coeff. | SE | P | | Coeff. | SE | P |
| VF (n=391) | 13 | | 3.2 | 0.46 | 13 | | 3.2 | | 28 | | | | 28 | | | |
| | | -2.41 | 6 | 0 | | -2.39 | 6 | 0.464 | | -0.22 | 2.27 | 0.924 | | 0.13 | 2.26 | 0.954 |
| MH (n=389) | 13 | | 1.2 | 0.16 | 13 | | 1.2 | | 28 | | | | 28 | | | |
| | | -1.72 | 3 | 2 | | -1.15 | 2 | 0.348 | | -1.10 | 0.85 | 0.197 | | -1.30 | 0.84 | 0.125 |
| LM (n=390) | 13 | | 1.2 | 0.04 | 13 | | 1.2 | | 28 | | | | 28 | | | |
| | | -2.59 | 8 | 4 | | -2.60 | 8 | 0.044 | | -1.18 | 0.89 | 0.184 | | -1.08 | 0.89 | 0.225 |
| DS (n=389) | 13 | | 3.9 | 0.01 | 13 | | 3.8 | | 28 | | | | 28 | | | |
| | | -9.78 | 0 | 3 | | -9.66 | 6 | 0.013 | | 0.06 | 2.71 | 0.982 | | 0.86 | 3.86 | 0.748 |

Note. SE=standard error; Coeff=unstandardized coefficient; CIQ=childhood IQ (outcome in childhood); BW=birth weight; LBW=low birth weight; HBW=high birth weight; Cognition in mid-life (outcome estimated by 4 cognitive tests): VF=Verbal Fluency test; MH Mill Hill Vocabulary scale; DS=Digit Symbol Test; LM=Wechsler Logical Memory test. Cognitive scores by birth weight group compared with normal birth weight group (2.49 kg ≤ BW < 4.08 kg).

Table 2. The effects of gestational age on cognitive functions across the life-course

| Cognition | Pre-term (GA < 37 weeks) | | | | | | | | Post-term (GA ≥ 42 weeks) | | | | | | | |
|--------------------|--------------------------|---------------|-----------|----------|----------|---------------|-----------|----------|---------------------------|---------------|-----------|----------|----------|---------------|-----------|----------|
| | Unadjusted | | | | Adjusted | | | | Unadjusted | | | | Adjusted | | | |
| | N | Coeff. | SE | P | N | Coeff. | SE | P | N | Coeff. | SE | P | N | Coeff. | SE | P |
| Childhood | | | | | | | | | | | | | | | | |
| CIQ age 7 (n=431) | 14 | | 3.9 | 0.00 | 14 | | 3.7 | | 102 | | | | 102 | | | |
| | | -12.33 | 5 | 2 | | -11.07 | 6 | 0.003 | | 0.50 | 1.65 | 0.763 | | -0.13 | 1.57 | 0.932 |
| CIQ age 9 (n=428) | 14 | | 4.2 | 0.01 | 14 | | 4.1 | | 100 | | | | 100 | | | |
| | | -10.21 | 3 | 6 | | -9.35 | 1 | 0.024 | | -1.13 | 1.78 | 0.527 | | -1.74 | 1.74 | 0.316 |
| CIQ age 11 (n=364) | 13 | | 3.0 | 0.15 | 13 | | 3.0 | | 86 | | | | 86 | | | |
| | | -4.38 | 5 | 1 | | -3.82 | 5 | 0.212 | | 0.04 | 1.33 | 0.976 | | -0.05 | 1.33 | 0.971 |
| Mid-life | | Coeff. | SE | P | | Coeff. | SE | P | | Coeff. | SE | P | | Coeff. | SE | P |
| VF (n= 391) | 13 | | 3.2 | 0.26 | 13 | | 3.2 | | 88 | | | | 88 | | | |
| | | -3.68 | 7 | 1 | | -3.90 | 6 | 0.231 | | -0.05 | 1.40 | 0.973 | | -0.43 | 1.40 | 0.760 |
| MH (n=389) | 13 | | 1.2 | 0.28 | 13 | | 1.2 | | 88 | | | | 88 | | | |
| | | -1.31 | 4 | 8 | | -1.06 | 2 | 0.386 | | 0.02 | 0.53 | 0.976 | | 0.07 | 0.53 | 0.901 |
| LM (n=390) | 13 | | 1.2 | 0.00 | 13 | | 1.2 | | 88 | | | | 88 | | | |
| | | -3.76 | 8 | 3 | | -3.81 | 8 | 0.003 | | -0.63 | 0.55 | 0.252 | | -0.78 | 0.55 | 0.158 |
| DS (n=389) | 13 | | 3.9 | 0.01 | 13 | | 3.8 | | 88 | | | | 88 | | | |
| | | -9.96 | 0 | 1 | | -10.31 | 5 | 0.008 | | 2.66 | 1.67 | 0.113 | | 1.95 | 1.65 | 0.240 |

Note. SE=standard error; Coeff. =unstandardized coefficient; GA=gestational age; CIQ=childhood IQ (outcome in childhood); Cognition in mid-life (outcome estimated by 4 cognitive tests): VF=Verbal Fluency test; MH Mill Hill Vocabulary scale; DS=Digit Symbol Test; LM=Wechsler Logical Memory test; Cognitive scores by gestational age group compared with birth at term (37 weeks ≤ GA < 42 weeks).

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