Association between erythrocyte sedimentation rate and IQ in Swedish males aged 18–20

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Abstract

Objective: To investigate if signs of inflammation are associated with performance on a contemporaneous IQ-test in males aged 18–20.

Design: Cohort study using data from the conscript register on performance on an IQ-test and on erythrocyte sedimentation rates (ESR) measured in 1969/70. Data on cardiovascular risk factors measured at conscription and national register data on childhood circumstances at age 10 were considered as potential sources of confounding. Data from national registers was linked to the cohort in order to explore long-term associations between ESR at age 18–20 and mortality between the years 1971–2006.

Setting: 49,321 Swedish males aged 18–20, screened for general health and for mental and physical capacity at compulsory conscription examination before military service.

Results: We found an inverse correlation between ESR and performance on an IQ-test. While an association was observed across IQ bands and ESR ranges, independent of cardiovascular risk factors or childhood circumstances, the association was slightly attenuated by adjustment for childhood socioeconomic position (SEP). An association between childhood SEP and ESR was detected that remained after adjusting for IQ. The ESR was also associated with future mortality following adjustment for childhood SEP.

Conclusions: Low-grade inflammation, as indicated by the ESR, is associated with reduced cognitive abilities already at age 18–20.

1. Introduction

In middle-aged and elderly individuals, poor cognitive function has been associated with increased base-line levels of inflammatory markers, e.g. C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Kuo et al., 2005). Chronic inflammatory processes, have also been associated with later cerebro- and cardio-vascular disease (Casserly and Topol, 2004; Wilson, 2008), suggesting that cerebrovascular changes can contribute to cognitive impairments in older individuals. Luciano and coworkers (2009), recently reported on a significant association between IQ at age 11 and levels of inflammatory markers at age 70 indicating a potential reverse causation in the association between IQ and inflammation in older individuals. It is, however, not known if levels of inflammatory markers are associated with cognitive function already in young individuals.

In Swedish males aged 18–20, cognitive function has for decades been determined by a standardized IQ test distributed during a screening procedure of future conscripts. The IQ test-results at the conscription examination have been associated with different health outcomes in studies where these young men have been followed for more than 30 years. For instance, low IQ scores have been reported to predict coronary heart disease, suicidal behavior, excessive alcohol consumption (Hemmingsson et al., 1998, 2006) and psychiatric illnesses e.g. schizophrenia (David et al., 1997; Zammit et al., 2004). Therefore, a better understanding of the causes of low IQ scores that may be involved in the development of these disorders is warranted.

The ESR is traditionally used as a very general indicator of disease. The ESR reflects the plasma levels of acute phase proteins (primarily fibrinogen and globulins) that contribute to aggregation of erythrocytes and their increased rate of sedimentation in a test tube. Since the ESR is determined by the rate of synthesis and half-life of these proteins it raises and declines more slowly than other inflammatory markers such as CRP or specific cytokines that better reflect rapid changes in inflammatory processes (van Leeuwen and van Rijswijk, 1994).

In the present study, we used the 1969/70 Swedish military screening cohort to investigate if the ESR, a general marker of inflammation determined during the medical screening procedure...
of all individuals, was associated with performance on the IQ test. Some aspects of cognitive performance are reported to be reduced during an acute infection (Smith, 1990) and could therefore potentially contribute to a coincident ESR–IQ association in this cross-sectional sample. We therefore explored the potential long term associations between ESR and socioeconomic position (SEP) at age 10 and between ESR and future mortality during a follow-up period of 35 years using data obtained from national registers. Since childhood SEP appears to influence levels of inflammatory markers (Nazmi and Victora, 2007), performance on IQ-tests (Kaplan et al., 2001) and future mortality (Hemmingsson and Lundberg, 2005) we also considered this variable as a potential confounder. Factors such as height, weight, blood-pressure and smoking that are associated with cardiovascular risk (Danesh et al., 2004), inflammation (Nayha, 1987) and IQ (Hemmingsson et al., 2007), potentially reflecting both early-life circumstances and life-style (Batty et al., 2009), were also considered in the ESR–IQ association.

2. Methods

2.1. Study population

The study was based on data from a nation-wide survey of 49,321 Swedish males, born 1949–51, who underwent a 2-day screening procedure in 1969/70 before compulsory military service. The background of the Swedish conscription surveys and the variables included has been presented in detail elsewhere (Ahlborg et al., 1973). In 1969/70, only 2–3% of all Swedish men were exempted from conscription, in most cases due to severe handicaps or congenital disorders. Those included in this study accounted for 97.7% of all conscripts in 1969/70, the remaining 2.3% were born before 1949.

2.2. Exposure assessment

At conscription, all men went through a physical examination. During this examination, venous blood was taken for determination of the ESR and hematocrit (Ahlborg et al., 1973). The ESR is affected by the hematocrit (Htc, i.e. the proportion of whole blood made up by erythrocytes), we therefore corrected the ESR values for hematocrit according to the formula ESR × Htc/45 (Borawski and Mysliwiec, 2001). Htc-corrected ESR-values could be calculated for 46,389 individuals. Height, weight and resting systolic/diastolic blood pressure were also measured and were here analyzed as continuous variables. In the present study, body mass index (BMI) was calculated using body weight (kg) divided by height (m) squared and analyzed as a continuous variable. Smoking was reported in a questionnaire. In the analyses smoking was divided into the following four categories: (1) >20 cigarettes/day, (2) 11–20 cigarettes/day, (3) 1–10 cigarettes/day, and (4) nonsmokers.

The IQ tests performed included tests of logic/general intelligence, verbal tests of synonym detection, and further tests of visuospatial/geometric perception, and technical/mechanical skills on the basis of mathematics/physics problems. All the tests were progressive, starting with relatively simple questions that then became more difficult (Carlstedt, 2000; Hemmingsson et al., 2006; Zammit et al., 2004). The logic/general intelligence test consisted of 40 items and took 12 min. Subjects were presented with an array of shapes and letters in combination and were asked to ‘strike through the square under the longest word’ (out of five). The verbal IQ tests lasted for 7 min and consisted of 40 questions. The items consisted of rows of five words, and subjects were instructed to underline the odd one out of, say, ‘teapot, sandwich, milk, egg, meat’, or – with greater difficulty – ‘insist, request, question, believe, admire’. The visuospatial test took 40 min and involved the presentation of probe geometric shapes (e.g. an isosceles triangle bisected by a vertical line) followed by four items consisting of different pairs of triangles of different sizes and with different orientations. Subjects were asked to state which options they had to make up the probe item.

The outcome of each test was ranked 1–9 (Carlstedt, 2000). The standard-nine values were transformed into a composite standard-nine scale to measure general ability, corresponding to approximate IQ bands of <74, 74–81, 82–89, 90–95, 96–104, 105–110, 111–118, 119–126, >126 (Zammit et al., 2004). 49,262 men (99.9%) registered a score on cognitive ability. The IQ test used is included in the Swedish Enlistment Battery (SEB) that has been used in continuously updated versions since 1944 to allocate 18-year-old men to military positions (e.g. privates or officers) during their compulsory service. Over the years, the various versions of the battery have been influenced by changes in factor analytically derived models of cognitive ability. The SEB-67 used for this study represents a further development of earlier tests designed to measure general ability (Carlstedt, 2000). A subset of men who were tested at the conscription examination in 1965 was retested at time of military service between 1 and 4 years later. For those who were tested after one or 2 years the correlation between the tests was 0.89. For those who were retested after 3 years the correlation was 0.80, and after 4 years it was 0.84 (Ross, 1988). The correlation between the four subtests included in the overall IQ measure used in this study ranged from 0.5 to 0.75 (David et al., 1997). There is a strong association between IQ at age 18 and educational level, socioeconomic position, and income at age 40 in this cohort (Hemmingsson et al., 2007). The correlation between the IQ scale and level of education obtained was 0.55 which is in accordance with most other studies on the subject (Deary et al., 2007).

The conscripts and their parents, or other head of household when different from the parents, were linked to each other between censuses through their personal identification numbers using the Multi-generation register. Information on childhood socioeconomic position was obtained from the National Population and Housing Census of 1960 (response rate 99%), i.e. when the subjects were 9–11 years old. The classification into the following six socioeconomic groups was based on information on the occupation of the head of the household: (1) unskilled workers, (2) skilled workers, (3) assistant non-manual employees, (4) non-manual employees at intermediate or higher level, (5) farmers, and (6) those not classified in a socioeconomic group. We also used information concerning the head of the household on a measure of ‘crowded housing’ (in this census >2 people/room – kitchen not included – was classified as crowded) from the 1960 census data.

Information on mortality and age at death among the subjects between the years 1971 and 2006 was obtained from the National Cause of Death Register administered by the Centre for Epidemiology at the National Board of Health and Welfare in Sweden. The ethics committee at the Karolinska Institute, Stockholm, approved the study.

2.3. Data analysis

The association between ESR and cognitive ability was estimated using linear regression and linear regression coefficients (LRC’s) with 95% confidence intervals, in both univariate and multivariate models, were calculated. In the adjusted models, the association between ESR and IQ score was estimated adjusting for the effect of childhood socioeconomic circumstances and cardio-vascular disease risk factors. Associations between ESR and mortality 1971–2006 was also estimated using Cox regression with hazard ratios (HR’s) and 95% confidence intervals, in both univariate and multivariate (including childhood social circumstances) models using the PHREG-procedure in the SAS computer package. The
analyses are based on those 46,780 men with full information on all variables.

3. Results

3.1. ESR and IQ

The mean (±SD) hematocrit adjusted ESR values in the current population of men aged 18–20 was 3.2 ± 3.8 mm (range 0–90 mm) during the first hour. As can be seen from Table 1 the distribution of ESR values in four arbitrary ESR ranges 0–3, 4–6, 7–10, > 11 is skewed with 65.3% of individuals in the lowest range and only 4.1% of individuals having an ESR > 11. Table 1 also gives mean IQ (on the 9-band scale) and the proportions of individuals with low scores on the IQ test (i.e. in bands 1–3 on the nine-band scale) in these four ESR ranges. We also calculated odds ratios for performing poorly on the IQ test using individuals in the 0–3 mm ESR range as a reference. Individuals in the higher ESR ranges were more likely to perform poorly on the IQ test (i.e. scored in bands 1–3). For example, individuals with ESR > 11 had an OR of 1.38 (95% CI 1.24–1.54) to perform poorly on the IQ-test. To investigate if this association was confined only to those performing most poorly on the IQ test, we calculated the mean ESR values across all nine IQ bands. As can be seen from Fig. 1, the mean ESR increased in each IQ band below 9, except between bands 5 and 4 and consequently the slope of a linear regression of the data deviates significantly from zero (p < 0.001).

Next, we performed linear regression analyses on the association between ESR and IQ test performance and explored the potential impact of other factors on this association. As can be seen from Table 2, a significant association between ESR and IQ was observed, a unit increase in ESR caused a decrease in IQ performance by 0.025 units, 95% CI (0.030–0.020). Excluding the 4.1% of the individuals with an ESR > 11 who would be most likely to suffer from acute disease, strengthened the association, −0.035 (−0.045, −0.026). Adjusting for the different factors given in Table 2, only childhood SEP and body height somewhat attenuated the ESR–IQ association whereas adjustment for smoking, BMI or blood pressure had no effect or slightly strengthened the association. In the fully adjusted model, a significant association between ESR and IQ remained.

3.2. Exploration of the association between ESR, SEP and IQ

To further explore the impact of childhood SEP on the ESR–IQ association, we calculated mean ESR as well as the OR of having a high ESR (i.e. >7 mm) for each of the different categories of paternal occupations at age 10 using sons of fathers with a non-manual high level occupation as a reference. As can be seen from Table 3,

Table 1

<table>
<thead>
<tr>
<th>ESR mm/h</th>
<th>n (%)</th>
<th>Mean IQ</th>
<th>IQ 1–3 (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11</td>
<td>30,568 (65.3)</td>
<td>5.4</td>
<td>18.8</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>4–6</td>
<td>11,900 (25.4)</td>
<td>5.3</td>
<td>20.3</td>
<td>1.10 (1.06–1.16)</td>
</tr>
<tr>
<td>7–10</td>
<td>2413 (5.2)</td>
<td>5.1</td>
<td>22.1</td>
<td>1.22 (1.11–1.35)</td>
</tr>
<tr>
<td>&gt; 11</td>
<td>1899 (4.1)</td>
<td>5.0</td>
<td>24.2</td>
<td>1.38 (1.24–1.54)</td>
</tr>
<tr>
<td>All</td>
<td>46,780</td>
<td>5.3</td>
<td>19.5</td>
<td></td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>ESR mm/h</th>
<th>n (%)</th>
<th>Mean IQ</th>
<th>IQ 1–3 (%)</th>
<th>OR, crude (95% CI)</th>
<th>OR, adjusted* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11</td>
<td>30,568 (65.3)</td>
<td>5.4</td>
<td>18.8</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Non-manual high</td>
<td>2.88</td>
<td>1.46 (1.12–1.88)</td>
<td>1.31 (1.01–1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-manual intermediate</td>
<td>3.04</td>
<td>1.15 (0.96–1.38)</td>
<td>1.12 (0.94–1.34)</td>
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<tr>
<td>Non-manual low</td>
<td>3.07</td>
<td>1.25 (1.03–1.51)</td>
<td>1.19 (0.98–1.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skilled workers</td>
<td>3.30</td>
<td>1.43 (1.20–1.70)</td>
<td>1.31 (1.10–1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unskilled workers</td>
<td>3.31</td>
<td>1.49 (1.26–1.76)</td>
<td>1.33 (1.12–1.58)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmers</td>
<td>3.46</td>
<td>1.65 (1.37–2.00)</td>
<td>1.49 (1.24–1.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>3.37</td>
<td>1.46 (1.12–1.88)</td>
<td>1.31 (1.01–1.70)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for IQ.

** Including only the 95.9% with an ESR-value <11 in the analyses.
sons of non-manual high level workers had the lowest mean ESR whereas sons of farmers had the highest mean ESR. Sons of manual workers were all at increased risk of having a high ESR. Adjusting for IQ, differences between these categories only slightly attenuated this association. For example, sons of farmers had an OR of 1.49 (95% CI 1.24–1.80) to have a high ESR after adjustment for IQ.

Including only the 95.9% with an ESR-value <11 in the analyses.

Table 4

<table>
<thead>
<tr>
<th></th>
<th>ESR all</th>
<th>ESR &lt; 11*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>CI 95%</td>
</tr>
<tr>
<td>Crude</td>
<td>0–6</td>
<td>1 (= ref)</td>
</tr>
<tr>
<td></td>
<td>≥7</td>
<td>1.19</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0–6</td>
<td>1 (= ref)</td>
</tr>
<tr>
<td></td>
<td>≥7</td>
<td>1.19</td>
</tr>
</tbody>
</table>

* HR adjusted for childhood socioeconomic position.
* Including only the 95.9% with an ESR-value <11 in the analyses.

4. Discussion

In the present study on a cohort of 18- to 20-year-old Swedish males, we found an inverse correlation between ESR and performance on an IQ-test. This association was not confined to those with the lowest IQ or to those with the highest ESR (i.e. ≥11 mm) but was observed across IQ bands and ESR levels. The graded association between IQ and ESR was minimally attenuated by adjustment for childhood SEP or height, but not by BMI, smoking, blood pressure or childhood housing conditions.

4.1. The ESR–IQ association

A number of studies have previously associated increased levels of inflammatory markers (e.g. CRP or interleukin 6) to impaired cognitive function. The majority of these studies have been conducted on elderly individuals, reviewed in (Kuo et al., 2005). Of the few studies that have investigated this association in younger individuals, similar findings have been reported in middle aged, apparently healthy, individuals (Gimeno et al., 2008b), in middle-aged individuals diagnosed with schizophrenia (Dickerson et al., 2007) and in school children suffering from obstructive sleep apnea (Gozal et al., 2007). Experimental studies in both humans (Reichenberg et al., 2001) and rodents (Chen et al., 2008) suggest that acute systemic inflammation can directly impair cognitive functions, e.g. working memory. The current study indicates a graded association between an inflammatory marker and cognitive performance also in young individuals. While the latter studies appear to support a direct influence of inflammatory mediators on brain function, the former studies leave room for the involvement of more indirect mechanisms. Since chronic inflammation is a risk-factor also for cardio-vascular disease, vascular mechanisms have been forwarded as a potential mechanism underlying the cognitive deficits associated with inflammation, at least in elderly individuals. (Luciano and coworkers (2009), recently reported that although levels of inflammation were associated to cognitive abilities among 70-year-olds, these levels were more strongly associated with their childhood-IQ. Based on these findings it appears as if IQ determines lifetime pro-inflammatory exposures and thus the risk for future cardio-vascular disease and further cognitive decline at an older age. In the current study, adjustments for BMI, blood pressure or smoking only strengthened the association between ESR and IQ suggesting that cardiovascular mechanisms are not (yet) involved. Childhood SEP and, to a smaller extent, height, however, appeared to explain some of the association between ESR and IQ.

4.2. Potential causes of an elevated ESR

The causes of the variations in ESR observed in this cohort, within and above what can be considered a “normal” range (i.e. 0–10 mm (Miller et al., 1983)) are not known. Acute infection is, however, the most common cause of an elevated ESR (Lijjestrand and Olhagen, 1955). Indeed, cognitive impairment has been reported in association with both acute (Smith, 1990) and chronic infections. For example, cognitive impairment has been reported in individual chronically infected with Epstein-Barr virus (White et al., 1998), herpes simplex viruses (Dickerson et al., 2003; Pewter et al., 2007) and Toxoplasma gondii (Flegel et al., 2003). Furthermore, studies in elderly individuals report titers of IgG directed at cytomegalovirus to be correlated to both CRP levels and cognitive function (Aiello et al., 2006). Taken together, these studies suggest that infections can contribute to the ESR–IQ association observed here. Furthermore, chronic inflammatory conditions, neoplasms or diseases affecting kidney function could contribute to the large elevations in the ESR observed in some of the young men included here (Lijjestrand and Olhagen, 1955). It should however be noted that the ESR–IQ association observed here was strengthened by excluding individuals with ESRs ≥ 11 mm, indicating that it is not individuals with chronic inflammatory conditions or acute infections that contribute to the present findings.

The variations in ESR can also reflect gene-variants that influence base-line ESR, IQ and long-term health outcome. Indeed, variants of cytokine genes related to high inflammatory activity have previously been associated to low cognitive functions in the elderly (Baune et al., 2008; Krabbe et al., 2009). Genetic effects are also supported by the fact that adult IQ appears to be strongly influenced by genetic factors with heritability estimates in the 70–80% range, reviewed in (Plomin and Spinath, 2004). A strong genetic influence on the IQ-mortality association was also recently reported (Modig-Wenerstad et al., 2008). While it has not been studied for ESR, twin studies suggest a substantial degree of heritability for base-line levels of CRP, supporting that gene variants can contribute to variations in base-line levels of inflammatory markers (MacGregor et al., 2004; Su et al., 2008; Wessel et al., 2007). Interestingly, Marioni and coworkers (2010) recently verified an association between CRP gene variants and plasma CRP levels, as well as an association between such levels and cognitive abilities in elderly individuals. These investigators, however, did not find a direct association between such gene variants and cognitive abilities, suggesting that CRP does not directly affect cognition.

4.3. The association between childhood SEP and ESR

The association between ESR at age 18–20 and childhood SEP at age 10 observed in the current material is unlikely to be explained by acute disease (e.g. infection). In light of the findings of Luciano...
and coworkers (2009) described above, this association could potentially be explained by differences in performance on the IQ test between these groups. The association between childhood SEP and ESR was indeed somewhat attenuated by adjustment for IQ suggesting that behaviors (resulting in pro-inflammatory exposures) can, to a small extent, contribute to an increased ESR at age 18–20. The significant association between childhood SEP and ESR that remained after adjusting for IQ differences, however, suggest that exposures related to paternal occupation, but not to IQ, during childhood are important determinants of the levels of inflammation at age 18–20. This finding may indicate forward, rather than reverse, causality in the ESR–IQ association. Moreover, this observation supports previous findings of social inequalities in low grade chronic inflammation as indicated by both CRP (Gimeno et al., 2008a) and ESR (Nayha, 1987) levels in adulthood. Indeed, the highest ESR levels were observed among sons of farmers. These boys were probably more likely to be exposed to infectious agents (Ahlm et al., 1998; Weber and Rutala, 1999), allergens (Venier et al., 2006) or other substances than sons of fathers in non-manual positions (Linaker and Smedley, 2002; Nathell et al., 2000; Perry, 2003; Sternstrom et al., 2001). This notion is further supported by recent studies suggesting SEP gradients in both exposure to agents causing chronic infections (Dowd et al., 2009) and in the immune response to such infections (Dowd et al., 2008).

4.4. The ESR-mortality association

The association between ESR and future mortality observed in the current sample has been observed previously, although these studies have included mostly older individuals. For example, a mildly elevated ESR in middle-aged individuals has been reported to independently predict cardio-vascular disease by decades (Andresdottir et al., 2003; Ingelsson et al., 2005). Similar observations were previously also reported in a long-term follow-up of 1000 healthy men aged 18–33, where a persistently elevated ESR, exceeding 10 mm, was found to predict future disease, including myocardial infarction, by several years (Froom et al., 1984). Taken together, these findings further support the notion that the ESR in the current sample has prognostic value and does not merely represent coincident disease.

4.5. Strengths and limitations

This study is the first to date to investigate the association between IQ and ESR in a population based cohort of young individuals. Only a very small proportion of Swedish men were exempted from conscription, i.e. the cohort is highly representative of males born around 1950 in Sweden. Many studies on early-life factors and later health outcomes rely on retrospective information collected at some point of the subject’s adult life which may introduce bias (Kauhanen et al., 2006). In this study, all information was collected at the time point when the conditions reported were actually present, e.g. socioeconomic positions in childhood, i.e. at ages 9–11, was collected from census information based information from parents in 1960.

There are also some important limitations. ESR was only measured at one point in time and we were not able to separate those with a chronically increased ESR from those with a temporarily increased ESR (e.g. due to an acute infections at the time of conscription). However, as already discussed, exclusion of individuals with ESR > 11 mm, only strengthened the ESR–IQ association. Furthermore, the ESR was associated with childhood SEP measured many years earlier and to mortality followed for over 35 years after the time of measurement. Taken together, these observations suggest that it is not only individuals with a concurrent disease that contribute to the ESR–IQ association. This mis-classification of chronic inflammation is likely to be non-differential and the presented associations can therefore to some extent be underestimated.

Non-inflammatory causes of elevations in the ESR should also be considered. While some factors known to elevate the ESR such as age, pregnancy and female sex are excluded here, other factors or pathological conditions are potential sources of confounding (Jurado, 2001). Of these, only anemia was corrected for in the present study by using data available on the packed erythrocyte volume (i.e. hematocrit).

Data on other markers of inflammation (e.g. acute phase proteins or cytokines) does not exist in the current material. Blood was not stored and, hence, such markers cannot be analyzed retrospectively. Therefore we rely solely on the ESR as an indicator of inflammation in these individuals. Since only Swedish men were included in the cohort studied here, we do not know if the current findings apply also to women or to other nationalities.

5. Conclusions

In conclusion, we report a graded association between ESR and performance on an IQ-test among 18- to 20-year-old males. The ESR at this age was associated with childhood SEP as well as with an increased risk of mortality during a 35-year follow-up suggesting that the ESR–IQ association is not only explained by coincident disease. The specific causes of an elevated ESR in late adolescence and their relation to cognitive function and to specific future health outcomes remain to be further explored in future studies.

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