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THE ASSOCIATION OF ADIPOSITY REBOUND AGE AND COGNITIVE FUNCTION IN EARLY ADULTHOOD

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The prevalence of obesity is increasing worldwide among both adults and children. Obesity is a well-known risk factor for several diseases, including metabolic syndrome, type 2 diabetes and certain cancers. During childhood BMI increases twice: there is a strong increase in BMI during the first year of life, which is followed by a slow decrease in BMI during the next few years. The second increase in BMI occurs at around the age of 3-8 years, and this increase is called the adiposity rebound. According to previous studies, early adiposity rebound age is associated with obesity in later life, and obesity has in some studies been associated with lower cognitive function compared to normal weight. The purpose of this study was to find whether there is an association between adiposity rebound age and cognitive function in later life.

The analyses are based on the randomised controlled Special Turku Coronary Risk Factor Intervention Project (STRIP). The height and weight of the participants were measured annually, and the adiposity rebound age was defined for each child. Cognitive function was measured at age 26 years using Cambridge Neuropsychological Test Automated Battery (CANTAB).

We found an association between adiposity rebound at older age and better cognitive function in girls, specifically better cognitive flexibility. Adiposity rebound age explained 4.7 % of the variation in cognitive flexibility, while adiposity rebound age combined with socioeconomic status and adult BMI explained as much as 10 % of this variation.

Our results indicate that early adiposity rebound might link with slightly poorer performance in this particular cognitive domain.

Key words: adiposity rebound age, cognitive function, obesity

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1 INTRODUCTION

The prevalence of obesity is increasing worldwide. It is a well-known risk factor for several diseases, including metabolic syndrome, type 2 diabetes, cardiovascular diseases and certain cancers. Childhood obesity is associated with obesity in adulthood. Obesity may also associate negatively with cognitive function and a few studies have also found associations between childhood obesity and cognitive function in later life.

Adiposity rebound age is the age when child's BMI starts to increase after its lowest point, usually at age of 3-8 years. Early adiposity rebound age is associated with later obesity. We were interested in whether early adiposity rebound age associates with later cognitive function. This is an important topic, because cognitive function evolves from childhood until early adulthood, reaching its highest point approximately at age 25 years. Thus, it is important to try to find both effective means and specific age windows, when the risk factors could be targeted in order to support cognitive development and therefore improve cognitive function.

2 REVIEW OF LITERATURE

2.1 DEFINITION OF BODY MASS INDEX (BMI)

Body mass index (BMI) is a way to measure human obesity. BMI is calculated by dividing weight in kilograms with height in metres squared. Normal BMI in adulthood is 18.5 – 25 kg/m^2, BMI over 25 kg/m^2 is considered overweight and BMI over 30 kg/m^2 obesity.(1) BMI correlates with body fat percentage, but it doesn't take lean mass into account, which makes BMI an imprecise in some cases. BMI might seem relatively low if a person has low lean mass or BMI might show unintentionally high values for a person with high muscle mass. However, BMI over 30 kg/m^2 has a relatively good predictive value for obesity. (2)

BMI varies across childhood: It rises rapidly after birth and during the first year of life, decreases thereafter and starts to rise again in pre-school age.(3,4) Therefore, ISO-BMI is used for defining children's BMI. ISO-BMI describes what an individual's BMI would be in adulthood if his/her body size remains in the same track as in childhood. ISO-BMI is calculated with the same way as adult-BMI (kg/m^2), but the value is multiplied by an age- and sex dependent factor to get the ISO-BMI

value.(5) ISO-BMI calculator can be found online at https://www.kaypahoito.fi/xmedia/pgr/200.036.html in Finnish and at https://www.ebmfrance.net/xmedia/pge/200.036.html?lang=en in English.

2.2 Definition of adiposity rebound

During childhood, BMI increases twice. First, there is a strong increase in BMI right after birth when infant gains weight rapidly during the first year of life. This increase in BMI is associated with increasing size and proliferation of adipocytes during the first 1-12 months of life. At 2 years of age, adipocytes are relatively larger in obese children. The size of adipocytes increases steadily from childhood to adolescence and adulthood, whereas adipocyte number seems to reach its maximum in early childhood and remains stable after that.(6) As the adipocyte number remains stable but the child increases in height, BMI trajectory starts to decrease gradually for a few years until reaching its nadir at around age 6 years.(7) This phase is followed by the second increase in BMI and is called adiposity rebound.(3,4) Adiposity rebound age means the age of the child when adiposity rebound occurs i.e., when the BMI curve starts to increase again. There is great variation of the adiposity rebound age, the lowest point of BMI varying between ages 3-8 years.(7)

2.3 Overweight and obesity

Prevalence of both childhood and adulthood obesity have increased globally.(1) Obesity is getting increasingly common in developed countries but also in developing countries. It has a profound effect on the risk of several diseases, including metabolic syndrome, type 2 diabetes, cardiovascular diseases and certain cancers.(8) Therefore, it is important to find both effective means and specific age windows, when the risk factors could be targeted in order to tackle the epidemics of childhood and adulthood obesity.

2.3.1 Definitions of overweight and obesity in children

According to World Health Organization (WHO) criteria, under 5 years old children are overweight when their weight-for-height is more than 2 standard deviations (SD) above the median in the WHO Child Growth Standards. For 5 to 19-year-old children, BMI-for-age above +1 SD is defined as overweight and BMI-for-age above +2 SD as obesity. The latter are equivalent for adult BMI values of 25 kg/m^2 and 30 kg/m^2.(1) In Finland, ISO-BMI 25-30 kg/m^2 is defined as overweight and >30 kg/m^2 as obesity. Alternatively, in Finland weight-for height between +20% and +40% in children

aged >7 years and between +10% and +20% in children aged <7 years is defined as overweight, and >+40% and >+20%, respectively, as obesity. (9)

2.3.2 EPIDEMIOLOGY OF OVERWEIGHT AND OBESITY IN CHILDHOOD

In a WHO study conducted during the years 2018-2020, which included 33 European countries, 29 % of children (31 % of boys, 28 % of girls) aged 7-9 years were overweight and 12 % of children (14 % of boys, 10 % of girls) were obese.(10) The lowest prevalence of overweight in children between 7-9 years was 6 % in Tajikistan where the rate of obesity was only 1 % while the highest prevalence of overweight was in Cyprus, 43 %, where 19% were obese. In 2016, WHO estimated that global overweight and obesity prevalence among children and adolescents aged 5-19 years was approximately 18 %, while in 1975, it had been only 4 %. The global prevalence of obesity was estimated to be 6 % among girls and 8 % among boys aged 5-19 years, when in the 1975 it was < 1 % among all children. (1)

In 2018-2020, 29.5 % of Finnish children aged 5-9 years were overweight or obese and 11.7 % were obese. (11) Furthermore, there was no significant change in overweight or obesity prevalence from the previous obesity report published in 2015-2017. (12) In Finland, overweight and obesity is observed to be significantly more common among boys than girls. According to statistics from 2021 published by Finnish Institute of Health and Welfare (THL), 29 % of 2–16-year-old boys and 19 % of 2–16-year-old girls were overweight or obese; 9 % of boys and 4 % of girls in this age group were obese.(13) This is still markedly less than in the United States where 35.4 % of 2–19-year-old children and adolescents were overweight or obese, 19.3 % of were obese, and as many as 6.1 % were in fact severely obese.(14)

2.3.3 RISK FACTORS FOR CHILDHOOD OBESITY

Because most obese children become obese adults, it would be important to recognize the risk factors for obesity at a young age. Some well-known risk factors include fast food consumption and large portion sizes. A follow-up study which was conducted with healthy girls from age 8-12 years to age 11-19 years documented that eating fast food >2 times a week was associated with increasing BMI.(15)

Sugar intake is commonly regarded as harmful for health. According to a Korean study, total sugar intake alone isn’t significantly associated with adiposity or metabolic risk in elementary school aged

children. Instead, the risks varied depending on the source of sugar and the strongest evidence found was that consumption of fructose from fruit had beneficial effects to adiposity index. (16) The metabolic effects of fructose seem to depend on the source of fructose. Even though fructose from fruit seems to have beneficial effects, fruit juice is associated with higher risk of type 2 diabetes (17) and higher intrahepatic lipid content (18). This might be due to fruit including fiber, vitamins, flavonoids, and antioxidants, which have beneficial effects on metabolism. There was also an adverse association between sugar intake from beverages and metabolic risk. An association between sugar sweetened beverages and metabolic risk was found at the baseline but not between sugar sweetened beverages and adiposity. (16) However, a meta-analysis revealed that sugar sweetened beverages consumption and BMI had a positive association in children.(19)

Dietary fat intake has also often been connected to obesity. Consuming food of high energy density and low physical activity are associated with obesity in children.(20) However, the relationship data between fat intake and body fat vary on children. A study with 1.5 – 4.5 years old children found no correlation between body fat and dietary fat percentage of total energy consumption. The authors hypothesized that the relation might develop later and not being evident yet in pre-school aged children.(21)

Food portion sizes are considered as a possible reason for increasing obesity prevalence. A U.S. study revealed that total energy intake of children aged 2-18 years old has increased by 184 kcal per day from 1977 to 2006 (22) This corresponds, depending on the age of the child, to approx. 10-15% increase in daily energy intake. They studied the portion sizes of selected food, which included soft drinks, fruit drinks, desserts, French fries, burgers, pizzas, hot dogs and Mexican fast food and found that portion sizes of all these foods had increased from 1977. (22) Greater portion sizes and energy intake indeed are proven to increase body weight. (23)

Greater physical activity level in preschool children is associated with lower body fat and seems to have greater effect on body fat than dietary composition. (21) A study on 8-13 years old Danish children added four additional physical education lessons to normal school curriculum, which included two physical education lessons per week. The control group had 1.5 hours of physical education lessons per week whereas the target group had in total of 4.5 hours of physical education lessons per week. Two years of this intervention tended to lower mean BMI values and total fat percentage, but, however, the differences remained insignificant. Importantly, the intervention had a significant effect on the prevalence of overweight and obesity and the effect was greater on subjects who were obese or overweight at the baseline. (24)

Decreased exercise and spending more time at home with technology are risk factors for developing obesity. A study from U.S. concluded that watching more TV or videos and playing games, as well as high calorie intake and low physical activity are independently associated with greater increase in BMI during a one-year follow-up of children aged 9-14 years. The changes were small, but the cumulative effects of these estimates would lead to a significant weight gain over the years.(25) A study on Korean overweight children aged 9-13 years found out that spending more time studying after school and habitual eating without hunger increased risk to develop obesity. (26)

Parental obesity is a well-known strong risk factor for childhood obesity. A meta-analysis showed that parental obesity was significantly associated with childhood obesity. (27) The association was stronger in older than younger children and in high-income countries than middle-income countries. The association was also stronger when both parents were obese compared to only one parent being obese. Even though maternal obesity has been considered to have greater association in children's obesity compared to paternal obesity (28), this meta-analysis showed no significant difference between obesity in mother-child pairs and father-child pairs.(27)

The association between childhood obesity and gut microbiota has also been studied. In 2013, a Belgian study found out that obese children had elevated Firmicutes-to-Bacteroidetes ratio, lower B. vulgatus and higher Lactobacillus spp. rates compared to lean children.(29) In obese children also the diversity of gut microbiota has found to be lower.(30) Faecal microbiota transplantations have been studied for being a potential treatment for obesity. A study conducted in 2019 found no significant weight loss on adolescents after faecal microbiota transplant. However, faecal microbiota transplant reduced visceral adiposity which is an important finding for treating obesity and obesity-related complications.(31)

2.4 CORRELATION BETWEEN EARLY ADIPOSITY REBOUND AND OBESITY

Childhood weight alone does not always predict adolescent obesity. Instead, numerous of studies have shown that early adiposity rebound leads to obesity in adulthood (7,32) Therefore, adiposity rebound age might be a better way to evaluate which children are at risk of becoming obese adolescents and adults.

The first study to find relationship between adiposity rebound and later obesity was published in 1984. The study was conducted with a sample of 151 children. This study defined early adiposity

rebound to occur before age 5.5 years and that such an early adiposity rebound associated with later obesity. Late adiposity rebound was defined to be after 7 years.(7)

In the STRIP study, children were followed from the age of 7 months and were categorized into normal weight group and overweight group based on their BMI at the age 13 years. Height and weight were measured annually, the BMI values were calculated, and the adiposity rebound age was determined. The study revealed that girls who were overweight at the age of 13 years had adiposity rebound age at 3.81 years whereas normal weight girls had adiposity rebound at the age of 5.46 years. Also, boys that were overweight at 13 years of age had adiposity rebound at the age of 4.30 years and boys who were normal weight had adiposity rebound at the age of 5.60 years. (32) It is of interest also that the adiposity rebound seems to occur earlier nowadays that before (7,32).

2.5 COGNITIVE FUNCTION

Cognitive function is defined as "the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses." Cognitive functioning is important in everyday life, as it is involved in mental processes such as thinking, attention, language, learning, memory and perception, therefore affecting our thoughts and behaviour. Cognitive function is processed in our brain, where neurotransmitters play a role in adjusting these functions. (33)

Cognitive function domains operate synergically, but they are divided into social cognition, executive function, memory, attention and psychomotor speed. Social cognition means reacting to emotionally charged stimuli. Executive function includes high level thinking and decision making and is required in mental flexibility, working memory, planning and response inhibition. Memory is divided into episodic memory, recognition memory and working memory. Attention is about staying focused in specific tasks and ignoring inappropriate stimuli. Psychomotor speed means the ability of noticing the presence of a stimulus and reacting to it. (33)

2.5.1 MEASUREMENT OF COGNITIVE FUNCTION

Cognitive function can be measured with intelligence quotient (IQ) score, which is evaluated by different cognitive tests.

As mentioned above, cognitive function domains operate synergically, which makes it complicated to test distinct cognitive processes separately. However, a lot of tests are available. Traditional tests are carried out by pencil and paper method, but now there's also developed computerized testing. Computerized testing minimizes errors and makes measurements more accurate.(33)

For example, Wechsler's IQ-tests are commonly used for evaluating intelligence. Wechsler's IQ-tests are traditional pen and paper tests and there are different standardized tests for children and adults. Tests include various tasks about logical reasoning such as numerical, linguistic and visual perception. The points of individual tasks are then converted into standardized points and compared to person's age group to get the IQ score. Normal IQ is 100 and standard deviation is 15, which means that IQ 70 (-2 SD) is considered as mental retardation. (34) For adults there is Wechsler Adult Intelligence Scale Fifth Edition (WAIS-V) (35) and Wechsler Intelligence scale for children (WISC) is used to test children's intelligence quotient (IQ) at the age of 6 – 16.9 years. For children aged 2 years and 6 months to 7 years and 7 months there is Wechsler Preschool and Primary scale of Intelligence Fourth Edition (WPPSI-IV).(36) The full-scale intelligence quotient (FSIQ) is derived from the primary index scale scores: verbal comprehension index (VCI), visual spatial index (VSI), fluid reasoning index (FRI), working memory index (WMI) and processing speed index (PSI). (37)

Cambridge Neuropsychological Test Automated Battery (CANTAB) is a computerized test battery, where suitable subtests can be selected based on the purpose of use. The difficulty level can be adjusted for all ages. CANTAB tests are language independent and culturally detached. The advantage of computerized CANTAB-tests, compared to traditional pencil and paper tests, is the ability to measure specific cognitive abilities, reduce human errors and collect more data points, which makes the tests more sensitive. CANTAB tests are divided into four categories: attention and psychomotor speed, emotion and social cognition, executive function and memory. These categories consist of smaller subtests. These tests can be selected to be suitable for assessing neurocognitive dysfunctions, such as autism, Alzheimer's, ADHD, etc. (38) CANTAB-tests were used in STRIP-study to evaluate cognitive function.

2.5.2 CAUSES OF ALTERED COGNITIVE FUNCTION

There are a lot of different factors which can affect children's cognitive function and therefore IQ. A study that was conducted in healthy Iranian children aged 6 – 7 years, found out that IQ was associated with household income, place of residence, previous education, delivery type, infant feeding and parent's educational degree.(39) Better socioeconomic status, parents' education, breastfeeding and living in bigger cities seemed to have a positive correlation with IQ. Data also showed that children

born by caesarean section had higher IQ than vaginally delivered children, which differed from previous studies. When these factors were taken into account in the analyses, lower IQ was associated also with higher BMI in children. (39)

A study conducted in Danish children collected information about potential predictors for later IQ with questionnaires, birth records and clinical examinations from pregnancy to childhood. At 7 years of age, they tested children's FSIQ with WISC-V-test and found out that mean FSIQ in scores were 2.8 points higher among girls than among boys. Lower FSIQ scores were present in children with maternal prepregnancy overweight and obesity compared to normal weight mothers. Breastfeeding, greater head circumference, longer maternal and paternal education, female sex were associated with higher FSIQ scores.(40)

Another study that tested 5 years old Danish children with WPPSI-R, had similar results, finding positive correlation between child's IQ and maternal IQ, parental education, female sex, longer breastfeeding and greater head circumference. What also seemed to have correlation with IQ were maternal BMI and maternal smoking during pregnancy.(41)

2.6 AGE AT ADIPOSITY REBOUND AND SUBSEQUENT COGNITIVE FUNCTION

There are no prior studies specifically focused on the association between adiposity rebound age and cognitive function measured in adulthood.

2.7 A HYPOTHESIS OF ENERGETIC TRADE-OFF BETWEEN ADIPOSE TISSUE AND BRAIN DEVELOPMENT

The hypothesis of energetic trade-off suggests that the high costs of human brain development require compensatory slowing of body growth rate.(42) C. W. Kuzawa et al calculated the human brain's glucose use from early childhood to adulthood. The resting metabolic rate of brain was 19.1 % for males and 24.0 % for females of the total resting metabolic rate. The brain's share of daily energy requirement was 10.9 % for males and 15.0 % for females. Developing human brain need even relatively more energy than adult brains. However, the peak of the brain energy consumption does not seem to be immediately after birth, but, interestingly, later in early childhood. Right after birth, the brain glucose uptake was 52.5 % and 59.8 % of resting metabolic rate, in males and females, respectively, dropping to 37.5 % and 40.8 % during the first 6 months of life. The peak of the brain

energy consumption takes place at age of 4.2 – 4.4 years, being 66.3 % and 65.0 % in males and females. Respective peaks were found calculating the brain's share of daily energy requirement, being 43.3 % in 3.8 year-old boys and 43.8 % in 4 year-old girls. There was an inverse correlation between body growth and brain glucose uptake, which supports the hypothesis of energetic trade-off between fat deposition and brain development in early childhood.(42) For our study, this seems remarkable as the brain energy consumption peaks at the adiposity rebound age when the BMI reaches its lowest point.

A longitudinal study conducted with children from North Carolina and Pennsylvania followed children through their early childhood measuring BMI regularly from 7 to 60 months of age and assessing executive functions at 36, 48 and 60 months of age. The study found out that greater decline in BMI values from age 24 to 60 months was associated with greater increase in executive functions at age 36 to 60 months. This finding supports the hypothesis of energy-trade-off between brain and adipose tissue. (43)

2.8 THE ASSOCIATION BETWEEN CHILDHOOD OBESITY AND ADULTHOOD COGNITION

There are only just a few studies about the relation of childhood obesity and cognition. The Dunedin Multidisciplinary Health and Development Study has followed prospectively children in New Zealand from birth to age 38 years, when cognitive function was evaluated. The study showed that subjects with lower IQ in adulthood were also obese as adults and these adults also had lower IQ in childhood. There was, however, no association between childhood obesity and later IQ decline. (44)

A study from year 2012 examined the association between BMI and academic performance and cognitive function with a sample of 2,519 children aged 8 – 16 years from The NHANES III, a cross-sectional survey of the US civilians that was conducted in 1988 – 1994. The block-design and digit-span subtests from WISC-R and the reading and arithmetic sections from WRAT-R were used to measure academic performance and cognitive function in the children. The association of academic performance and BMI was not significant after adjusting for parental socioeconomic status. However, the association between impaired cognitive function and higher BMI was significant after including all the covariates. Children with overweight had lower visuospatial organization and general mental ability than normal weight subjects.(45)

A Finnish study investigated the association between cardiovascular risk factors in childhood and midlife cognitive performance at age 34 to 49 years. Cognitive function was evaluated with

computerized CANTAB tests, which revealed an association between childhood overweight and obesity and lower results in visual processing and sustained attention in midlife. Also, high systolic blood pressure and high serum total cholesterol were associated with lower performance in midlife episodic memory and associative learning. (46)

The association between midlife obesity and impairment in cognitive function in later life has also been widely studied. A meta-analysis showed that obesity in midlife was associated with decreased cognitive function which manifests as dementia and Alzheimer's disease. However, the risk of dementia and Alzheimer's disease was also higher for underweight subjects compared to normal weight subjects. (47)

Taken together, data on childhood adiposity development and future cognitive performance is still limited and urges further research.

3 AIMS AND HYPOTHESIS

Most of the previous studies have focused on the association between obesity and cognitive function or between adiposity rebound age and later obesity. There are also some studies about childhood obesity and later cognitive function. However, there are no prior studies focusing specifically on the links between adiposity rebound age and cognitive function in adulthood. Thus, the aim of this study was to reveal if there is an association between adiposity rebound age and cognitive function in young adulthood, at age when cognitive function is estimated to have reached its peak. We hypothesized that adiposity rebound at older age might associate with better cognitive function in young adulthood.

4 MATERIALS AND METHODS

4.1 SUBJECTS AND METHODS

The randomised controlled Special Turku Coronary Risk Factor Intervention Project (STRIP) recruited children at age 5 months from well-baby clinics in Turku, Finland, via nurses. Children were randomly assigned by random numbers to either the intervention or control groups at study entry. Study group allocation was unmasked.

The aim of the intervention was to reduce exposure to known environmental cardiometabolic risk factors, particularly through diet. Intervention families met with the counselling team, including

nutritionists, nurses, and physicians at 1–3-month intervals until the child was aged 2 years, and twice per year thereafter. The control children were seen twice per year until age 7 years and annually thereafter. Similar measurements, including keeping of food diaries, were performed for both study groups, and they met the same study personnel. The outcomes were assessed by clinic and research staff.

The intervention group received individualised dietary counselling from age 7 months until age 20 years.(48,49) At the early phase of the intervention, breastfeeding was encouraged; breast milk or formula was suggested to be continued until age 12 months. Counselling was given to parents until the child was aged 7 years, and thereafter, gradually more information was given directly to the child. The dietary counselling aimed to increase the parents' and the children's nutrition knowledge and to support the beliefs that the child's diet could be modified and that making favourable dietary changes could improve health. The intervention consisted of 30 minutes individualised dietary counselling and nutrition education sessions led by a nutritionist. Each session had a specific dietary topic and involved performing tasks. The parents were informed of the sessions' topics and tasks and encouraged to discuss them at home. Furthermore, parents or children received oral and written feedback about the child's diet (written feedback given for the analysed food diary). The intervention group also received information on their serum cholesterol levels annually. The main target of the counselling was to replace saturated fat with unsaturated fat in the child's diet and concomitantly reduce the intake of cholesterol. Reduction in total fat intake was not targeted. The intervention group also received counselling on how to reduce salt intake and to favour wholegrain products, fruit, and vegetables. A fixed diet was never specified; the counselling was individualised, and the child's recent food diary was used as a basis of suggestions for dietary changes (e.g. replacement of dairy fat-blend spreads with vegetable oil-based spreads). The dietary recommendations were based on the latest version of the Nordic nutrition recommendations (e.g. 30% of energy intake from fat, <10% from saturated fat, 10–15% from protein, and 50–60% from carbohydrates).

Key nutritional targets of the intervention, reflecting nutrition recommendations, were the ratio of polyunsaturated and monounsaturated fat to saturated fat (indicative of dietary fat quality) of more than 2:1, and an intake of saturated fat less than 10% of energy, cholesterol less than 300 mg/day (age ≥18 years), and fibre more than 3 g/MJ or more than 25 g/day (age ≥18 years).(50,51)

As part of the intervention, primary prevention of smoking was introduced at age 8 years.(48) It was based on supporting the self-image of non-smoking children and on understanding the health risks associated with both active and passive smoking. Attitudes towards smoking, avoiding passive smoking, and the development of addiction were also discussed, and suggestions on related topics—

e.g. how to refuse offered tobacco—were discussed with the child. A physically active lifestyle was encouraged, but it was not a structured, continuous part of the intervention. The children in the control group received only the basic health education given at Finnish well-baby clinics and school health care. Topics related to the intervention were not discussed. To keep the control group participants motivated to stay in the study, they received information on their serum cholesterol levels.

The study was approved by the associated university and hospital district ethical authorities. Written informed consent was obtained from parents at study entry, and from the participants at ages 15, 18, and 26 years.

4.2 ANTHROPOMETRIC MEASUREMENTS

Heights and weights of the participants were measured by physicians or nurses from age 7 months, and waist circumference was measured beginning at age 7 years. Weights of the children were measured to the nearest 0.1 kg with an electronic scale (S10; Soehnle, Murrhardt, Germany) at each visit. Recumbent lengths of the children younger than 2 years were recorded, and thereafter, standing heights were measured to the nearest millimeter with a wall-mounted Harpenden stadiometer (Holtain, Crymych, United Kingdom). The BMI of each child was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Adiposity rebound, which is the age point at which the calculated BMI value of a child starts to increase again after an initial decrease,(7) was defined for each child. Data on birth weight and length were collected from the well-infant clinic records.

4.3 CANTAB COGNITIVE TESTS

Cognitive function was tested at the 26-year follow-up study clinical visit. Because blood sampling was part of the study protocol, the participants were instructed to fast overnight before the study visit and to avoid smoking, strenuous physical activity, and alcohol and coffee during the previous evening and the morning of the study visit. Before the cognitive testing, the participants were given a light snack consisting of a whole-meal oat-based biscuit, 2 dL of an oat drink, and weak fruit/berry juice.

Cognitive function was measured using the Cambridge Neuropsychological Test Automated Battery (CANTAB). A computerized, predominantly nonlinguistic, and culturally neutral test battery composed of several separate tests of a wide range of cognitive domains, CANTAB has been shown to distinguish cognitively healthy adults.(53) A suitable combination of separate tests can be selected

for each particular study and used as a cognitive testing battery, performed on a touch-screen computer system. For the STRIP 26-year follow-up study, six separate tests were selected in addition to the Motor Screening Test, which was used as a training/screening tool to indicate difficulties in test execution: (1) the Paired Associates Learning (PAL) test, which measures visual and episodic memory and visuospatial associative learning (hereafter learning and memory); (2) the Verbal Recognition Memory (VRM) test, which measures verbal memory with aspects of both immediate and delayed recall (hereafter verbal memory); (3) the Spatial Working Memory (SWM) test, which measures short-term and spatial working memory and problem solving (hereafter working memory); (4) the Reaction Time (RTI) test, which measures reaction and movement speed and attention (hereafter reaction time); (5) the Rapid Visual Information Processing (RVP) test, which measures visual processing, recognition, and sustained attention (hereafter information processing); and (6) the Attention Switching Task (AST) test (currently termed the Multitasking Test in the CANTAB test battery), which measures cognitive flexibility, set-shifting and inhibitory control (hereafter cognitive flexibility). The CANTAB tests included in the STRIP cognitive function test battery are described below.

The *Motor Screening (MOT) test* was used to introduce the participants to the CANTAB test battery and the device. In this test, colored crosses appeared on the screen in different locations and the participant had to press the cross as quickly and accurately as possible. The outcome measures assessed the participant's response speed and pointing accuracy.

At the beginning of the *Paired Associates Learning (PAL) test* "closed" boxes appeared on the screen. When the test began, the boxes on the screen started to open and close one at a time in a random order. Inside one or more boxes were pictures. The participant had to try and memorize which picture was located in which box. When all the boxes had opened and closed once, the pictures started to appear in the middle of the screen. At this point the participant had to remember which picture they had seen in which box. If the participant incorrectly located a picture, all the boxes opened in sequence again to remind the participant of where the pictures were. The outcome measures included the errors made by the participant, the number of trials required to locate the picture(s) correctly, memory scores, and the stages completed. The test assessed visual memory and new learning, which are related to medial temporal lobe functions. The test took eight minutes to complete.

At the beginning of the *Verbal Recognition Memory (VRM) test,* the participant was shown words one by one on the monitor. Then the participant tried to remember as many of these words as possible. In the next phase, VRM assessed verbal memory and new learning. It measured the ability to encode

and subsequently retrieve verbal information, with recall tapping into fronto-temporal networks and recognition assessing the hippocampal areas. The test took 10 minutes to complete.

At the beginning of the *Spatial Working Memory (SWM) test,* several colored boxes appeared on the screen. On the right side of the screen was an empty column with the number of levels corresponding to the number of boxes. The aim of the test was for the participant to find a yellow token in one of the boxes on the screen by selecting one box at a time and using a process of elimination to locate the token. Each time the participant found the token, he/she was supposed to place it in the column on the right side of the screen. In the following rounds, the token could not be in the same box as it has been earlier. As the column filled up, the test progressed to a more difficult level as the number of the boxes on the screen increased. The boxes added up to maximum of 12 on the screen at a time. The colors and location of the boxes changed each time, to discourage the use of stereotyped search strategies. Outcome measures included errors (selecting a box that had a token before or revisiting a box already found empty) and strategy. SWM requires retention and manipulation of visuospatial information. The test made notable demands on executive function and measured strategy as well as working memory errors. These functions are mainly associated with domains related to the frontal lobes. The test took four minutes to complete.

In the *Reaction Time (RTI) test* the participant had to hold their finger on a button at the bottom of the screen. At the top of the screen were one (simple mode) or five (five-choice model) circles, and a dot appeared in one of these circles in a random order. At this point, the participant had to release the button on which they are holding their finger and press the circle with the dot as quickly as possible. The outcome measures assessed both reaction time and movement time. RTI assesses motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy, and impulsivity. These functions were associated with domains related to the frontal and occipital lobes. The test took three minutes to complete.

In the *Rapid Visual Information Processing (RVP) test,* the participant was given one to three 3-digit sequences at the beginning of the test. In the middle of the screen was a white box. Digits from 2 to 9 appeared in the box in pseudo-random order at a rate of 100 digits/minute. The participant had to recognize whether a given number sequence appeared in the box and press a button in the center of the screen as fast as possible. The outcome measures covered latency (speed of response), probability of false alarms, and sensitivity. The test measured sustained attention. These functions are associated with domains related to the frontal and parietal lobes. The test took seven minutes to complete.

In the *Attention Switching Task (AST) test,* two buttons were shown on the screen, one on the left side and the other on the right. An arrow appeared on the screen, which indicated the right button to press. The arrow appeared on either the left or right side of the screen and pointed left or right. Depending on the task, the participant had to either push the button in the direction in which the arrow was pointing, or the button located on the same side of the screen as the arrow. A cue appeared at the top of the screen to indicate which rule the participant should follow. In some sections of the test, the rule above was consistent, whereas in other sections the rule varied between the two randomized ones. The test assessed the participant's ability to manage conflicting information and to ignore task-irrelevant information. It took eight minutes to complete.

Each of the CANTAB tests produced several variables. We first studied the distribution of each variable. At this point, the Motor Screening Test data were excluded from further analyses because of the ceiling effect (ie, all participants had the maximum score). To create cognitive function outcome variables that would gather all the data from each test into a single variable, we used a *z*-score–based classification of the cognitive variables within each test. First, all the individual variables in the cognitive function data were transformed into a standard deviation scale with a mean of 0 and SD of 1. After this, test-wise scores were calculated by summing the individual standardized variables within each separate test and then dividing the sum thus obtained by the number of variables in that particular test. This data reduction procedure resulted in six outcome variables, each representing one of the studied cognitive domains.

4.4 STATISTICAL METHODS

Differences between the means were studied with Student's t test. Spearman's correlation tests were used to study the correlations between adiposity rebound age and cognitive function domains. As the adiposity rebound age was non-normally distributed, a logarithmic transformation was performed and the transformed were used in linear regression analyses to study the associations between adiposity rebound age and cognitive function. Sex, socioeconomic status and adulthood BMI were used as covariates in the linear multivariable models. Finally, interactions between sex and adiposity rebound age were investigated by introducing multiplicative interaction term separately into the regression models containing all the main effects. The statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA), and the level of statistical significance was set at 0.05.

5 RESULTS

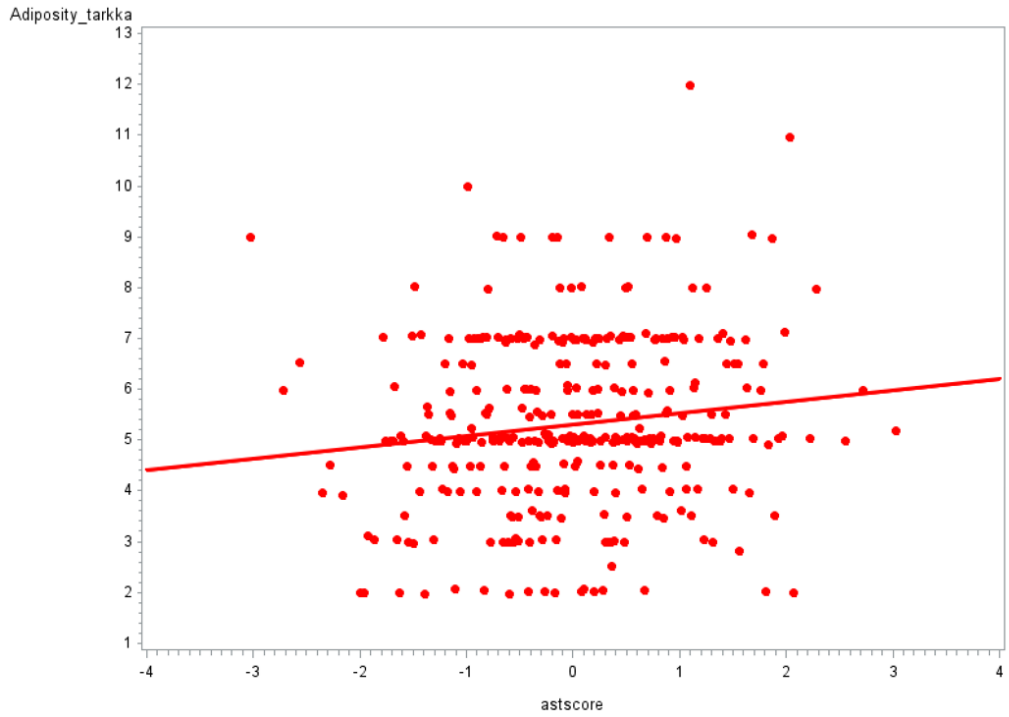
Adiposity rebound was determined from 628 children (309 girls and 319 boys). In our population, the mean age of adiposity rebound was 5.36 years (SD 1.70, range 1.96–12.02 years). The sex-specific mean adiposity rebound ages were 5.20 years (SD 1.83, range 1.96 – 11.97 years) in girls and 5.51 years (SD 1.55, range 1.99 – 12.02 years) in boys. The mean adiposity rebound age was statistically significantly higher among boys than girls (p=0.0029)

We analysed the correlation between adiposity rebound age and each measured cognitive domain using Spearman correlation analyses. Among the whole STRIP population, adiposity rebound age had positive correlation with cognitive flexibility (AST test) (β=0.14, p=0.009), linear regression on Figure 1. There was no correlation between adiposity rebound age and other cognitive domains (Table 1).

After the analyses for the whole population, we conducted sex-specific analyses (boys and girls separately). In girls, the positive correlation between adiposity rebound age and cognitive flexibility (AST test) remained significant (β=0.24, p<0.001), linear regression on Figure 2. Additionally, there was a positive correlation between adiposity rebound age and information processing (RVP test) (β=0.17, p=0.010) in girls. (Table 2).

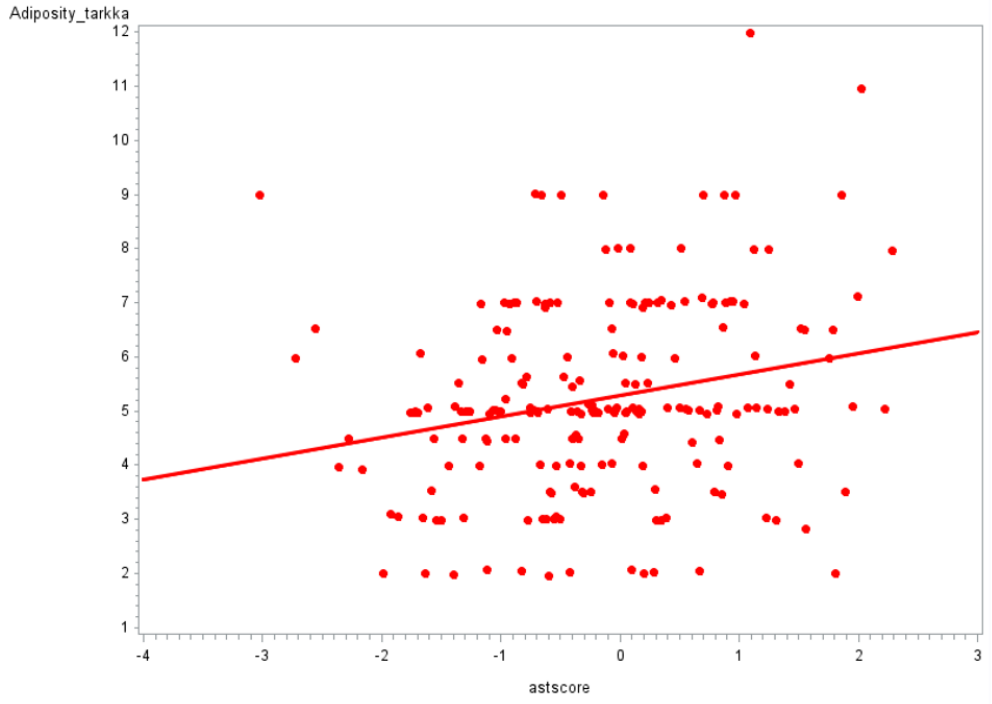
In boys, no correlations between adiposity rebound age and any of the studied cognitive domains were observed. For comparison, linear regression model for adiposity rebound age and cognitive flexibility in boys presented in Figure 3. See table 3 for details of each cognitive domain in boys.

1. Adiposity rebound age and cognitive flexibility among the STRIP cohort.



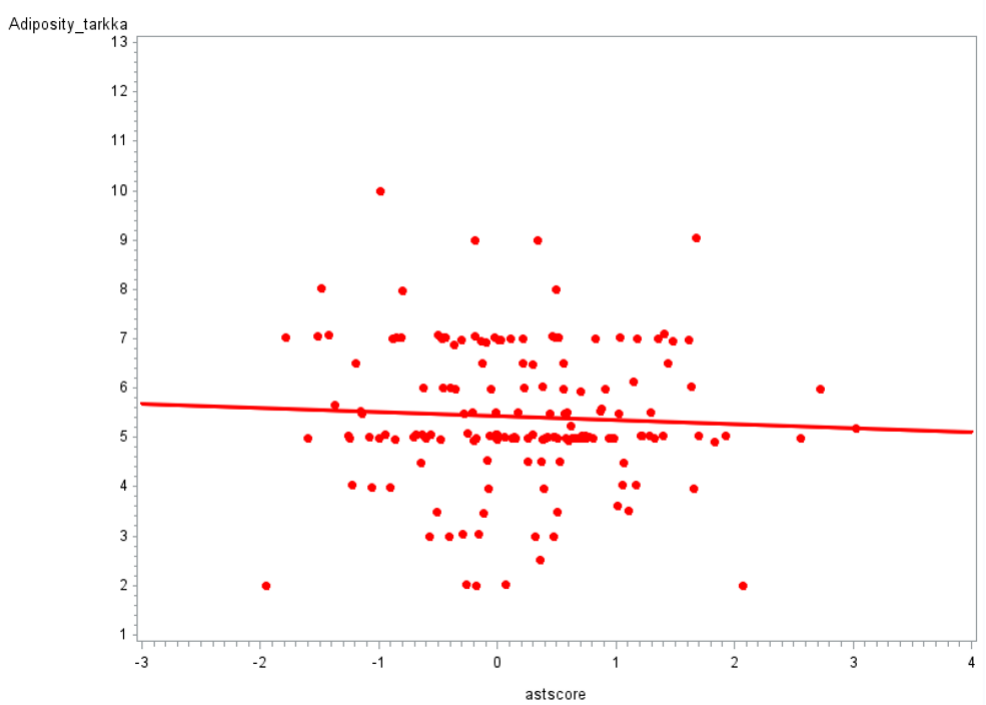
Adiposity_tarkka = the adiposity rebound age, astscore = cognitive flexibility (AST test)

2. Adiposity rebound age and cognitive flexibility in girls.



Adiposity_tarkka = the adiposity rebound age, astscore = cognitive flexibility (AST test)

3. Adiposity rebound age and cognitive flexibility in boys.



Adiposity_tarkka = the adiposity rebound age, astscore = cognitive flexibility (AST-test)

Table 1. Correlation between adiposity rebound age and cognitive domains among the STRIP cohort.

Cognitive domain	**N**	**Correlation coefficient**	**p value**
Learning and memory (PAL test)	542	-0.045	0.379
Verbal memory (VRM test)	542	0.078	0.121
Working memory (SWM test)	542	-0.035	0.483
Reaction time (RTI test)	541	0.085	0.093
Information processing (RVP test)	540	0.085	0.106
Cognitive flexibility (AST test)	500	0.136	0.009

The values are numbers of participants as well as correlation coefficients and p-values from Spearman's correlation analyses.

Table 2 Correlation between adiposity rebound age and cognitive domains in girls.

Cognitive domain	**N**	**Correlation coefficient**	**p value**
Learning and memory (PAL test)	220	-0.048	0.483
Verbal memory (VRM test)	220	0.087	0.199
Working memory (SWM test)	220	-0.061	0.370
Reaction time (RTI test)	220	0.114	0.114
Information processing (RVP test)	219	0.175	0.010
Cognitive flexibility (AST test)	205	0.241	<0.001

The values are numbers of participants as well as correlation coefficients and p-values from Spearman's correlation analyses.

Table 3 Correlation between adiposity rebound age and cognitive domains in boys.

Cognitive domain	**N**	**Correlation coefficient**	**p value**
Learning and memory (PAL test)	173	-0.036	0.638
Verbal memory (VRM test)	173	0.107	0.163
Working memory (SWM test)	173	-0.011	0.886
Reaction time (RTI test)	172	0.048	0.530
Information processing (RVP test)	172	-0.073	0.344
Cognitive flexibility (AST test)	160	-0.084	0.293

The values are numbers of participants as well as correlation coefficients and p-values from Spearman's correlation analyses.

Furthermore, we analyzed the association between adiposity rebound age and cognitive function domains using linear regression models. When adjusting for sex, the association between adiposity rebound age and cognitive flexibility remained significant ($p<0.001$). Subsequently, we studied the possible effect modification of sex for the found association by introducing a multiplicative interaction term (adiposity rebound age*sex) in the linear model. We observed a significant interaction for sex ($p<0.05$), and thus, conducted separate analyses for boys and girls. Details of the analyses for each cognitive domain on STRIP cohort presented on Table 4 and Table 5.

Table 4 GLM procedure linear model. The association between adiposity rebound age and cognitive domains among the STRIP cohort

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	393	-0.20	0.14	0.167	0.5 %
Verbal memory (VRM test)	393	0.23	0.15	0.130	0.6 %
Working memory (SWM test)	393	-0.08	0.15	0.596	0.01 %
Reaction time (RTI test)	392	0.16	0.15	0.276	0.3 %
Information processing (RVP test)	391	0.16	0.14	0.258	0.3 %
Cognitive flexibility (AST test)	365	0.41	0.15	0.009	1.9 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance model including only adiposity rebound age. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

Table 5 The association between adiposity rebound age and cognitive domains among the STRIP cohort.

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	314	-0.36	0.16	0.027	2.8 %
Verbal memory (VRM test)	314	0.09	0.17	0.612	3.7 %
Working memory (SWM test)	314	-0.08	0.17	0.640	0.3 %
Reaction time (RTI test)	313	0.24	0.17	0.165	0.7 %
Information processing (RVP test)	312	0.11	0.16	0.497	1.5 %
Cognitive flexibility (AST test)	295	0.54	0.17	0.002	4.7 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance from a model including adiposity rebound age, socioeconomic status and adult BMI. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

In girls, we observed a significant direct association between adiposity rebound age and cognitive flexibility (AST test; β=0.58, p=0.004). We observed that adiposity rebound age explained 4.1 % of the variation of cognitive flexibility (Table 6) When adiposity rebound age, BMI in adulthood and sosioeconomic status at age 13 were included simultaneously into linear regression model the association for adiposity rebound age remained unchanged (β = 0.59, p=0.007), and the model explained 10 % of cognitive flexibility in girls (Table 7).

In girls, there was also a weak direct association between adiposity rebound age and information processing (RVP test) (β=0.31), however the association failed to reach convetional statistical significance (p=0.085). For this cognitive domain, adiposity rebound age explained 1.4 % of the variance in information processing (Table 6). However, after adjusting for sosioeconomic status and adult BMI, the association diluted and did not reach statistical significance (β=0.20, p=0.304), (Table 7).

Table 6 GLM procedure linear model. The association between adiposity rebound age and cognitive domains in girls.

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	220	-0.16	0.18	0.369	0.4 %
Verbal memory (VRM test)	220	0.23	0.19	0.217	0.7 %
Working memory (SWM test)	220	-0.13	0.17	0.470	0.2 %
Reaction time (RTI test)	220	0.25	0.17	0.159	0.9 %
Information processing (RVP test)	219	0.31	0.18	0.085	1.4 %
Cognitive flexibility (AST test)	205	0.58	0.20	0.004	4.1 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance model including only adiposity rebound age. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

Table 7 The association between adiposity rebound age and cognitive domains in girls.

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	177	-0.25	0.20	0.216	1.2 %
Verbal memory (VRM test)	177	0.06	0.21	0.789	2.5 %
Working memory (SWM test)	177	-0.16	0.19	0.399	1.8 %
Reaction time (RTI test)	177	0.27	0.19	0.167	1.5 %
Information processing (RVP test)	176	0.20	0.20	0.304	3.9 %
Cognitive flexibility (AST test)	169	0.59	0.21	0.007	10 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance from a model including adiposity rebound age, socioeconomic status and adult BMI. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

In boys, there was no association between adiposity rebound age and cognitive flexibility (AST test; β=-0.06, p=0.808) or any other cognitive domain in the unadjusted analyses. (Table 8) However, after adjusting the analyses for sosioeconomic status and adulthood BMI, adiposity rebound age was negatively associated with learning and memory (PAL test; β=-0.55, p=0.049). This model explained 6.2 % of the variance in learning and memory. (Table 9)

Table 8 GLM procedure linear model. The association between adiposity rebound age and cognitive domains in boys

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	173	-0.25	0.25	0.306	0.6 %
Verbal memory (VRM test)	173	0.35	0.24	0.155	1.2 %
Working memory (SWM test)	173	-0.05	0.26	0.853	0.02 %
Reaction time (RTI test)	172	0.05	0.27	0.866	0.02 %
Information processing (RVP test)	172	-0.16	0.24	0.494	0.3 %
Cognitive flexibility (AST test)	160	-0.06	0.25	0.808	0.04 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance model including only adiposity rebound age. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

Table 5 The association between adiposity rebound age and cognitive domains in boys.

Cognitive domain	**N**	**β estimate**	**standard error**	**p value**	**R^2**
Learning and memory (PAL test)	137	-0.55	0.27	0.049	6.2 %
Verbal memory (VRM test)	137	0.36	0.29	0.219	4.7 %
Working memory (SWM test)	137	-0.11	0.30	0.711	2.5 %
Reaction time (RTI test)	136	0.22	0.32	0.504	9.5 %
Information processing (RVP test)	136	-0.21	0.29	0.473	1.0 %
Cognitive flexibility (AST test)	126	0.15	0.28	0.594	0.8 %

The numbers are numbers of participants, β estimates, standard errors, p-values and proportions of explained variance from a model including adiposity rebound age, socioeconomic status and adult BMI. PAL test = Paired Associates Learning test; VRM test = Verbal Recognition Memory test; SWM test = Spatial Working Memory test; RVP test = Rapid Visual Information Processing test; RTI test = Reaction Time test; AST test = Attention Switching Task test.

6 DISCUSSION AND CONCLUSION

In this follow-up study we found an association between higher adiposity rebound age and better cognitive function, specifically better cognitive flexibility. Our participants were cognitively healthy. In girls, we found a direct association between adiposity rebound age and attention switching task test (AST) which measures cognitive flexibility and inhibitory control, being called the "Multitasking test". It assesses set-shifting and inhibition, i.e. the participants ability to manage conflicting information and to ignore task-irrelevant information. Thus, it may be considered as a complex and difficult test. This means that early adiposity rebound might link with poorer performance in this particular cognitive domain, which means that by affecting to adiposity rebound age in childhood, we could plausibly promote cognitive health later in life.

The observed associations were relatively weak as adiposity rebound age explained 4.7 % and adiposity rebound age combined with socioeconomic status and adult BMI explained 10 % of the variation in cognitive flexibility (AST test). However, cognitive health is affected by many factors, and knowing these factors is important for future children to promote the brain development, which happens in early childhood. This is important as by achieving the maximum potential of the brain early in life, the decline of cognitive function in old age could be smoother, potentially improving quality of life even to the old days. This topic is especially important because the prevalence of obesity is increasing all around the World and the association between obesity and impaired cognitive function is already well-known. These findings support the Finnish Current Care Guidelines about preventing obesity in all age-groups.

Some factors that are present in adult obese individuals including e.g. the low-degree inflammation of blood vessels in the brain due to obesity being a proinflammatory state might explain the association between obesity and cognitive decline.(45) There is also evidence that impaired brain insulin signaling might cause cognitive decline (54) and Alzheimer disease in late-life. (55) Insulin resistance with or without diabetes is also associated with cognitive decline. (56,57) Research shows that obesity and diabetes can affect cognitive function via leptin hormone. Leptin is a peptide hormone that is secreted by adipose tissue. Excessive production of leptin can lead to Leptin receptor deficiency, which causes lower levels of leptin in the brain, leading to impaired learning and memory.(58) It is hypothesized that the association between obesity and cognitive decline can be partly due to sleep apnea, which is often a consequense of obesity, causing hypoxemia which leads to cognitive decline.(59)

This study brings a new perspective for cognitive health. The mechanism of the association between adiposity rebound age and cognitive function remains unknown. From this point of view, the theory about energy trade off between adipose tissue and brain seems interesting as the adiposity rebound age i.e. the age-point when the BMI starts to increase again after its lowest point happens around the same time as the peak metabolism of the brain. It’s also unknown, why the association is prominent only on girls population.

This study has its strengths but also some limitations. Strengths include a large group of subjects, the subjects were examined at the same age and the measurements of weight, height and cognitive function were precise. Limitations include the dropouts during the 26-year follow-up.

In conclusion, we found that age at adiposity rebound associates with cognitive function in girls. These associations were relatively subtle. However, we found, for the first time, an association

between obesity development in childhood and later cognitive function. This finding further supports the benefits of life-long maintenance of normal weight.

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