Risk Factor Profile in Youth, Genetic Risk and Adulthood Cognitive Function: The Cardiovascular Risk in Young Finns Study

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ABSTRACT

Introduction: The role of risk factor profile in childhood and adolescence on adulthood cognitive function and whether it differs by genetic risk is still obscure. To bring this evidence, we determined cognitive domain specific youth risk factor profiles leveraging the childhood/adolescence data from the Cardiovascular Risk in Young Finns Study, and examined whether genetic propensity for poor cognitive function modifies the association between the risk profiles and adulthood cognitive function.

Methods: From 1980, a population-based cohort of 3596 children (age 3-18 years) have been repeatedly followed-up for 31 years**.** Computerized cognitive test measuring: 1) memory and learning, 2) short-term working memory, 3) reaction time, and 4) information processing was performed for N=2026 participants (age 34-49 years). Cognitive domain specific youth risk profile scores including physical and environmental factors were assessed from the data collected at baseline and categorised into favourable, intermediate, and unfavourable. A polygenic risk score for poor cognitive function was categorised into low, intermediate, and high risk.

Results: At all genetic risk levels, a favourable youth risk factor profile associated with better learning and memory, short-term working memory and information processing compared to unfavourable risk profile (e.g. β=0.501SD, 95%CI 0.043-0.959 for memory and learning among participants with high genetic risk). However, no significant interactions were observed between the youth risk factor profile score and genetic propensity for any cognitive domain (P>0.299 for all).

Conclusion: A favourable youth risk factor profile may be beneficial for cognitive function in adulthood irrespective of genetic propensity for poor cognitive function.

INTRODUCTION

Cognitive function begins to develop from infancy, reaches its peak in early adulthood and, after that, declines along whole adulthood [1-3]. It has been suggested that the age-related decline in cognitive function may be slower among persons with high level of cognitive function in young adulthood [4]. Thus, finding childhood and adolescence determinants for young adulthood cognitive function, and thereof, optimizing the peak level of adulthood cognitive function is important [5,6]. Noticeably, while the importance of primary prevention of cognitive deficits by treating risk factors in midlife is acknowledged by the *Lancet* Commission [7], only little is known about the possibilities for primordial preventive means earlier during the life-course. Addressing this evidence gap, better understanding of the youth, i.e. childhood and adolescence, determinants for adulthood cognitive function is needed.

We have previously provided evidence that cumulative burden of youth cardiovascular factors, including elevated blood pressure, high serum total-cholesterol concentration and smoking from childhood and/or adolescence, is adversely related to adult cognitive function [8]. Nonetheless, a comprehensive assessment of youth risk factor profile of physical and environmental factors with cognitive function in adulthood is not yet available. Additionally, whether the role of a favourable youth risk factor profile is more pronounced for those individuals who have genetic propensity for poor cognitive function in adulthood has remained unknown. To bring this novel evidence, we leveraged the data from the Cardiovascular Risk in Young Finns Study to examine the association of various youth risk factors and genetic propensity for poor cognitive function with cognitive function in adulthood and tested whether the association of youth risk factor profile with adulthood cognitive function differs by genetic risk.

METHODS

Participants

The Cardiovascular Risk in Young Finns Study (YFS) is an ongoing multi-center population-based cohort study to assess risk factors underlying cardiovascular diseases [9]. In 1980 (baseline), 4,320 children aged 3-18 years were randomly selected from the population register of all five university cities with medical schools and their rural surroundings in Finland. Altogether, 3,596 (83 %) of the invited children participated in the baseline survey. In 2011, 2,063 individuals from the original cohort participated in the 31-year follow-up, and 2,026 (98 %) of them underwent cognitive testing. All participants provided written informed consent, and the study was approved by local ethics committees. Formation of the study population is shown in the Figure 1.

Cognitive function

Cognitive function was measured in 2011 by a computerized cognitive testing battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom), with details described elsewhere [8,10]. Briefly, the test battery in the YFS included: 1) motor screening test (MOT) used as a training/screening tool to indicate difficulties in test execution; 2) paired-associates learning (PAL) test measuring visual and episodic memory and visuospatial associative learning (hereafter memory and learning); 3) spatial working memory (SWM) test measuring short-term and spatial working memory and problem solving (short-term working memory); 4) reaction time (RTI) test measuring reaction and movement speed and attention (reaction time); and 5) rapid visual information test (RVP) measuring visual information processing, recognition, and sustained attention (information processing). The validity of the test battery has been previously studied comparing the individual outcome variables derived from each subtest to traditional pen-and-paper tests. These comparisons have provided correlation

coefficients ranging between 0.12 and 0.26 for the RVP test [11], between 0.47 and 0.69 for the PAL test [12-14], 0.80 for the RTI test [15], and between 0.16 and 0.28 for the SWM test [11]. Additionally, the prior studies have reported good test-retest reliability for the test battery (correlation coefficients ranging between 0.71 and 0.89) [16,17]. Detailed information on the cognitive testing is given in the Supplemental material.

Each test produced several variables. Principal component analyses were conducted separately for all individual tests to identify components accounting for most of the variation within the dataset. The first principal components identified from these analyses for each test were used to represent cognitive function in the specific cognitive domains. The MOT test component was excluded from further analyses because all participants had the maximum score. Other components were normalized using a rank order normalization procedure resulting in four variables, each with mean 0 and standard deviation 1.

Polygenic risk score

Genotyping was performed for N=2442 samples collected in the follow-up studies in 2001, 2007 or 2011 using custom build Illumina Human 670k BeadChip at Welcome Trust Sanger Institute. Genotypes were called using Illuminus clustering algorithm [18]. Genotype imputation was done using Beagle software10 [19] and population-specific The Sequencing Initiative Suomi (SISu) as reference data (www.sisuproject.fi). A polygenic risk score for cognitive function was calculated using LDpred, a Bayesian method that estimates posterior mean causal effect sizes from GWAS summary statistics by assuming a prior for the genetic architecture and linkage disequilibrium (LD) information from a reference panel [20]: an infinitesimal fraction of causal variants was assumed and summary statistics from Savage et

al [21] GWAS for intelligence were used. The LD between markers was estimated from the SISu data. A higher score indicates an increased risk of poor cognitive function.

Youth risk factors from participants

All youth measures were conducted at baseline unless otherwise stated. Participants' height and weight were measured and body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Data on birth weight was verified from the well-baby clinic records. Blood pressure, serum total-cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using standard methods, with details described elsewhere [22]. Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald [23]. Serum insulin levels were measured using a modification of the immunoassay method of Herbert et al [24]. Serum high-sensitive C-reactive protein (CRP) concentrations were measured by an automated analyzer (Olympus AU400) using a turbidimetric immunoassay kit ("CRP-UL"-assay, Wako Chemicals, Neuss, Germany) [25].

Youth smoking was defined as smoking daily and alcohol use defined as any use of alcohol (including very small amounts, such as half a bottle of beer) using available data from baseline and the subsequent 3- and 6-year follow-ups if participants were aged ≤18 years at the time of survey; those aged<12 years at all three time points were considered non-smokers and having no alcohol use. An age-standardized physical activity index was calculated [26], and shown to be reliable and valid [27]. Briefly, we used a parent-completed questionnaire to collect data about the amount and vigorousness of their child's play time and the child's general level of activity as compared with other children for participants aged 3 and 6 years. A self-reported questionnaire to ask about intensity and frequency of physical activity during leisure time was applied for those aged 9 to 18 years [28]. The frequency of fruit and

vegetable intake was assessed by a questionnaire asking habitual dietary choices during the past month; a binary variable was generated for fruit and vegetable consumption (≤once a week coded as 0 and otherwise 1). Youth school performance was measured as the mean of grades in all individual school subjects; data for those who were not of school age at baseline were obtained from the subsequent 3- and 6-year follow-ups.

Youth risk factors from parents

Parents were asked to record their height and weight on a self-reported questionnaire [29] and BMI was calculated as mentioned above. Pre-pregnancy weight was asked for pregnant women. Parents were asked if they had been diagnosed of the following diseases: diabetes, hypertension, myocardial infarction, coronary heart disease and stroke. Socioeconomic status (SES) was determined using three variables: the length of the parent's education (in years for the parent with the highest education), mean household income and any history of parental unemployment. Education and income variables were standardized and then multiplied by -1. SES was defined as the mean of the three variables (higher score indicates lower SES).

Statistical analysis

Mean (standard deviation) or number (%) were used to describe participants' youth characteristics. Characteristics between participants who were lost to follow-up and those who remained in the study were compared using Student t-test and Chi-square test, as appropriate. Potential youth risk factors were selected based on findings of previous research [8, 30-36]. Three analytical steps were conducted to obtain the final multivariable model separately for each cognitive domain. First, age and sex adjusted linear regression was used to examine associations of each youth risk factor and genetic risk with all cognitive domains. Second, a multivariable model was constructed including age, sex and those youth risk

factors with age and sex-adjusted p-value<0.1 in the previous step. Third, a backwards stepwise modelling approach was applied to the multivariable model; youth risk factors with p-value ≥0.05 were removed in a stepwise manner starting from the factor with the largest p-value until all youth risk factors remaining in the model had p-values<0.05.

Subsequently, weighted domain specific youth risk factor profile scores were generated as the sum of variables in the final multivariable models multiplied by corresponding beta coefficients (excluding age and sex). The scores were used to classify participants into favourable (highest quintile), intermediate (quintile 2-4), and unfavourable (lowest quintile) youth risk profile. Additionally, sensitivity analyses were conducted for the youth risk factor profile scores using quartile and quintile based categorization. Participants were also classified into low (lowest quintile), intermediate (quintiles 2-4), and high (highest quintile) genetic risk groups based on the polygenic risk scores values.

Age and sex adjusted linear regressions were used to examine the associations of youth risk factor profiles and genetic risk with the cognitive domains in adulthood. The association of the youth risk factor profile groups and cognitive function was also estimated stratified by genetic risk groups. Interactions between youth risk factor score and genetic risk were tested by including a product term in age and sex adjusted models separately for each cognitive domain. Furthermore, we also combined the youth risk factor profile and genetic risk groups (9 groups with favourable and low risk as reference) and studied the combined associations with cognitive function. Moreover, the interactions of youth risk factor profile score with age and sex were tested. All analyses were conducted in Stata 14.0 (Stata Corporation, Texas, USA) and a two-tailed p value<0.05 was considered statistically significant.

RESULTS

This study comprised 2,025 participants who had data on at least one of the cognitive domains and at least one of the youth risk factors or polygenic risk score. Compared to those who were retained, those who were lost to follow-up were younger and more likely to be males but less likely to have used alcohol and to have paternal history of myocardial infarction. The non-participants also had lower BMI and insulin levels but poorer school performance and more disadvantaged SES (Supplemental Table 1).

In the age and sex adjusted analyses, genetic propensity for poor cognitive function associated negatively with all other cognitive domains except reaction time (learning and memory: β=-0.173SD; working memory β=-0.125SD; information processing β=-0.199SD; p-value for all <0.001; reaction time β=-0.003SD, p=0.915; Supplemental Table 2). The Supplemental Table 2 shows the age- and sex-adjusted associations of each separate youth risk factor with the studied cognitive domains.

Based on the age and sex adjusted associations presented in the Supplemental Table 2, we constructed the cognitive domain specific multivariable models (Table 1). In these analyses, the association of genetic risk remained for all cognitive domains that showed association already in the age and sex adjusted analyses. The youth risk factors which association remained in the multivariable model for learning and memory were age, systolic blood pressure, school performance, maternal BMI and paternal myocardial infarction. For short-term working memory the associations of age, sex, birth weight, school performance and paternal stroke persisted, while the factors remaining associated with adulthood information processing were sex, school performance, paternal myocardial infarction and socioeconomic

status. Finally, sex, physical activity, school performance and paternal myocardial infarction remained associated with reaction time after applying the multivariable approach.

Subsequently, domain specific youth risk factor profile scores were created based on those variables that remained significantly associated ($p<0.05$) with cognitive function in the multivariable models. Subsequently, the analyses were run entering the youth risk factor profile score (divided into unfavourable/intermediate/favourable) and genetic risk score (divided into high/intermediate/low) into a same age and sex adjusted model separately for each cognitive domain (Table 2). In these analyses, a more unfavourable youth risk factor profile was associated with poorer function in adulthood in all studied cognitive domains compared to a favourable youth risk factor profile. Similarly, higher genetic risk was associated with poorer performance on memory and learning, short-term working memory and information processing compared to low genetic risk (Table 2). Sensitivity analyses applying either quartile or quintile based classification for the youth risk factor profile scores obtained similar results (Supplemental tables 3 and 4).

Table 3 shows the associations of the youth risk factor profiles with cognitive function within the levels of genetic risk (low/intermediate/high). Collectively, regardless of the level of genetic risk a more favourable youth risk factor profile was observed to associate with better cognitive function; the point estimates ranged between β=0.247SD in short-term working memory for the group having intermediate genetic risk and intermediate youth risk factor profile and β=0.906SD in information processing for the group with low genetic risk and favourable youth risk factor profile (Table 3).

No significant interactions were observed between the domain specific youth risk factor scores and genetic risk ($p \geq 0.299$ for all, Figure 2). The analyses for the variable combining the youth risk factor score and genetic risk levels showed that compared to the group with low genetic risk and favourable youth risk factor profile all other groups had worse learning and memory, short-term working memory and information processing; the point estimates ranged between β=-1.355SD for learning and memory for those with high genetic risk and unfavourable youth risk factor profile and β=-0.233SD in short-term working memory for those with intermediate genetic risk and intermediate youth risk factor score (Supplemental table 5). Finally, similar systematic combined associations were not observed for reaction time.

A significant interaction between age and youth risk factor profile was observed for information processing ($p=0.015$). For age stratified analyses the participants were dichotomised into younger (baseline age 3-9 years) and older (baseline age 12-18) groups. There was an association between youth risk factor score and information processing in both age groups, but the associations were somewhat stronger among the younger (younger: β=0.364, 95%CI 0.283, 0.446; older: β=0.313, 95%CI 0.251, 0.375; $p<0.001$ for both). No other interactions between youth risk factor profile and age or sex were found (p-value>0.35 for all).

DISCUSSION

We identified several factors in childhood and adolescence that contributed to adulthood cognitive function: systolic blood pressure, physical activity, maternal BMI, paternal myocardial infarction and stroke, birth weight, school performance and socioeconomic status. Both an unfavourable youth risk factor profile and high genetic risk were independently

associated with poorer cognitive function in adulthood. There was no significant interaction between youth risk factor profile score and genetic risk. Importantly, a favourable youth risk factor profile was significantly associated with better cognitive function within all genetic risk levels. These findings suggest that a favourable youth risk factor profile may offset genetic risk of poor cognitive function in adulthood. As cognitive function in midlife is strongly associated with cognitive deficits in later life [5], our study provides novel evidence for primordial prevention of cognitive deficits beginning from childhood.

As a higher level of cognitive function and activities in midlife have been associated with lower later life risk of dementia [2,6], the clinical importance of the associations observed for youth risk factor profile could be estimated by relating to late life dementia risk. For example, participants with an unfavourable youth risk profile had 0.573SD lower score for memory and learning. This translates into an approximately 28% higher risk of dementia in later life based on the Atherosclerosis Risk in Communities Study by Knopman et al [2]. The risk increases to 80% among participants with both an unfavourable youth risk profile and high genetic risk.

No studies have comprehensively examined the risk factors measured in youth that associate with cognitive function in adulthood. In the Young Finns Study cohort, we have previously shown links between cumulative burden of childhood cardiovascular factors, including elevated blood pressure, high serum total-cholesterol concentration, and smoking with adulthood cognitive function [8]. Other studies have identified additional childhood determinants, such as low SES [30-33], adverse childhood events [37], and blood lead levels [38]. However, several youth factors, such as parental BMI and cardiovascular diseases, have not been studied or have only been studied with cognitive function in childhood/adolescence

[34-36]. Of note, maternal BMI and paternal myocardial infarction and stroke may have shared genetic and environmental background and these novel findings suggest that the prevention of cognitive deficits may begin as early as in prior generations.

Polygenic risk scores have been increasingly used in research but debate continues on its clinical utility. Previous studies have mainly focused on polygenic risk scores for Alzheimer's disease and linked it to cognitive function [39-42] or to Alzheimer's disease [43,44]. Using polygenic risk score for cognitive function based on the latest summary statistics of GWAS [21], we showed strong associations of the score with several cognitive domains in cognitively healthy middle-aged adults. Importantly, we showed that a favourable youth risk factor profile comprised of physical/environmental factors was associated with better cognitive function in adulthood, regardless of genetic risk. These findings have important public health and clinical implications as they suggest that genetic risk of poor cognitive function in adulthood could possibly be offset by achieving a favourable risk profile as early as in childhood and adolescence. Adopting a favourable youth risk factor profile might eventually help to optimize cognitive development, and thereof, boost adulthood cognitive function which could potentially reflect even in reduced risk of cognitive deficits or postponed clinical cognitive deficits later in life.

The main strength of this study is the youth-onset long-term prospective follow-up of a large population-based cohort, allowing us to examine the early-life exposures with adult cognitive function in a nationally representative Finnish cohort. Our study has limitations. As with all single country studies, the findings may not be generalizable to other areas of the world. Moreover, similar to all population-based studies with long follow-up time, we had missing data due to loss to follow-up after an extensive study period of 31 years. We showed that

participants who were lost to follow-up were younger and more likely to be males and had lower BMI, poorer school performance and more disadvantaged SES. Thus, our results may be more generalizable to children who are older, females and have had better living conditions. Finally, CANTAB may be criticized for low validity found in previous studies comparing the CANTAB to traditional pen-and-paper tests [11-15]. It should be kept in mind, that the validity has been analyzed mainly applying single variables derived from the CANTAB subtests each of which produce several outcome variables. It is also noticeable, that comparison between the CANTAB and pen-and-paper tests inevitably reflect also the innate differences in the test types such as the different types of stimulus and response (e.g. visual and auditory stimuli vs. motor and oral responses).

In conclusion, both an unfavourable youth risk profile and high genetic risk were independently associated with poorer cognitive function in adulthood. The observed lack of interaction between youth risk factor profile score and genetic risk underlines the importance of adopting a favourable risk factor profile at all genetic risk levels. Our current results highlight that childhood and adolescence are important time-windows for promotion of adulthood cognitive health, and thereof, also hold the potential for primordial prevention of later cognitive decline**.**

STATEMENTS

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Statement of Ethics

The study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Young Finns Study was approved by the 1st ethical committee of the Hospital District of Southwest Finland and by local ethical committees (1st Ethical Committee of the Hospital District of Southwest Finland, Regional Ethics Committee of the Expert Responsibility area of Tampere University Hospital, Helsinki University Hospital Ethical Committee of Medicine, The Research Ethics Committee of the Northern Savo Hospital District and Ethics Committee of the Northern Ostrobothnia Hospital District). All participants gave written informed consent, and informed consent of every participant under the age of 18 was obtained from a parent and / or legal guardian.

Conflict of interest

The authors declare nothing to disclose and no conflict of interest with respect to this manuscript.

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Author Contributions

F.W., C.G.M., O.T.R, and S.P.R. were involved in study design. S.P.R., M.J., P.S., T.Le., K.P, P.T., L.T., E.J., N.H-K., M.K., T.La., J.S.A.V., and O.T. R. were responsible for data collection and management. A.A-O. performed the analyses for the genetic data. F.W. performed data analysis and drafted the manuscript, in consultation with J.O.H. and S.P.R.. All authors revised manuscript content and approved the final manuscript and had access to the data. J.S.A.V. contributed to the initial design of Young Finns. O.T.R. leads Young Finns and contributed to obtaining funding and to the study design. O.T.R. and S.P.R. are the guarantors of the study and accept full responsibility for the finished article, had access to any data, and controlled the decision to publish.

Data Availability Statement

All data generated or analyzed during this study are included in this article [and/or] its supplementary material files. Further enquiries related to the data can be directed to the principal investigator of the Young Finns Study, Professor Olli Raitakari.

REFERENCES

1. Cheng ST. Cognitive Reserve and the Prevention of Dementia: the Role of Physical and Cognitive Activities. In *Current Psychiatry Reports* (2016; Vol. 18, Issue 9). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-016-0721-2

2. Knopman DS, Gottesman RF, Sharrett AR, et al. Midlife vascular risk factors and midlife cognitive status in relation to prevalence of mild cognitive impairment and dementia in later life: The Atherosclerosis Risk in Communities Study. Alzheimers Dement 2018;14:1406-1415.

3. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med 2013;29:737-752.

4. Stern Y, Barulli D. Cognitive reserve. In *Handbook of Clinical Neurology* (2019; Vol. 167, pp. 181–190). Elsevier B.V. https://doi.org/10.1016/B978-0-12-804766-8.00011-X

5. Rajan KB, Wilson RS, Weuve J, Barnes LL, Evans DA. Cognitive impairment 18 years before clinical diagnosis of Alzheimer disease dementia. Neurology 2015;85:898-904.

6. Najar J, Ostling S, Gudmundsson P, et al. Cognitive and physical activity and dementia: A 44-year longitudinal population study of women. Neurology 2019;92:e1322-e1330.

7. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. Lancet 2017;390:2673-2734.

8. Rovio SP, Pahkala K, Nevalainen J, et al. Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance: The Young Finns Study. J Am Coll Cardiol 2017;69:2279-2289.

9. Raitakari OT, Juonala M, Ronnemaa T, et al. Cohort profile: the cardiovascular risk in Young Finns Study. Int J Epidemiol 2008;37:1220-1226.

10. Rovio SP, Pahkala K, Nevalainen J, et al. Cognitive performance in young adulthood and midlife: Relations with age, sex, and education-The Cardiovascular Risk in Young Finns Study. Neuropsychology 2016;30:532-542.

11. Smith PJ, Need AC, Cirulli ET, Chiba-Falek O, Attix DK. A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with "traditional" neuropsychological testing instruments. J Clin Exp Neuropsychol 2013;35:319-328.

12. Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Computerized delayed matching to sample and paired associate performance in the early detection of dementia. Appl Neuropsychology 1995;2:72-78.

13. Kim C, Lee JY, Ha TH, et al. The usefulness of the Cambridge Neuropsychological Test Automated Battery (CANTAB) for assessing cognitive functions in the elderly: A pilot study. J Korean Ger Soc. 2009;13:69-78.

14. Torgersen J, Flaatten H, Engelsen BA, Gramstad A. Clinical validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian epilepsy population. J Behav Brain Sci 2012;2:108-116.

15. Sexton CE, McDermott L, Kalu UG, et al. Exploring the pattern and neuronal correlates of neuropsychological impairment in late-life depression. Psych Med 2012:42:1195-1202.

16. Gonçalves MM, Pinho MS, Simões MR. Effects of socio-demographic variables on performance on the Cambridge Neuropsychological Automated Test for the assessment of dementia and Portuguese norms for older adults living in retirement homes. Clin Neuropsychol 2016a;30:284-317.

17. Gonçalves MM, Pinho MS, Simões MR. Test–retest reliability analysis of the Cambridge neuropsychological automated tests for the assessment of dementia in older people living in retirement homes. Appl Neuropsychology:Adult 2016b;23:251–263.

18. Teo YY, Inouye M, Small KS, et al. A genotype calling algorithm for the Illumina BeadArray platform. Bioinformatics 2007;23:2741-2746.

19. Browning BL, Browning SR. A unified approach to genotype imputation and haplotype-phase inference for large data sets of trios and unrelated individuals. Am J Hum Genet 2009;84:210-223.

20. Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. Am J Hum Genet 2015;97:576-592.

21. Savage JE, Jansen PR, Stringer S, et al. Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence. Nat Genet 2018;50:912-919.

22. Porkka KV, Raitakari OT, Leino A, et al. Trends in serum lipid levels during 1980-1992 in children and young adults. The Cardiovascular Risk in Young Finns Study. Am J Epidemiol 1997;146:64-77.

23. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

24. Herbert V, Lau KS, Gottlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. J Clin Endocrinol Metab 1965;25:1375-1384.

25. Juonala M, Viikari JS, Ronnemaa T, Taittonen L, Marniemi J, Raitakari OT. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. Arterioscler Thromb Vasc Biol 2006;26:1883-1888.

26. Telama R, Viikari J, Välimäki I, et al. Atherosclerosis precursors in Finnish children and adolescents. X. Leisure-time physical activity. Acta Paediatr Scand Suppl 1985;318:169-180.

27. Telama R, Yang X, Leskinen E, et al. Tracking of physical activity from early childhood through youth into adulthood. Med Sci Sports Exerc 2014;46:955-962.

28. Juonala M, Pitkanen N, Tolonen S, et al. Childhood Exposure to Passive Smoking and Bone Health in Adulthood: The Cardiovascular Risk in Young Finns Study. J Clin Endocrinol Metab 2019;104:2403-2411.

29. Kivimaki M, Smith GD, Elovainio M, et al. Socioeconomic circumstances in childhood and blood pressure in adulthood: the cardiovascular risk in young Finns study. Ann Epidemiol 2006;16:737-742.

30. Aartsen MJ, Cheval B, Sieber S, et al. Advantaged socioeconomic conditions in childhood are associated with higher cognitive functioning but stronger cognitive decline in older age. Proc Natl Acad Sci U S A 2019;116:5478-5486.

31. Ayaz E, Shenkin SD, Craig L, et al. Early-life determinants of cognitive ability in childhood and old age. The Lancet 2012;380:S23.

32. Skogen JC, Overland S, Smith AD, Mykletun A, Stewart R. The impact of early life factors on cognitive function in old age: The Hordaland Health Study (HUSK). BMC Psychol 2013;1:16.

33. Everson-Rose SA, Mendes de Leon CF, Bienias JL, Wilson RS, Evans DA. Early Life Conditions and Cognitive Functioning in Later Life. American Journal of Epidemiology 2003;158:1083-1089.

34. Contu L, Hawkes CA. A Review of the Impact of Maternal Obesity on the Cognitive Function and Mental Health of the Offspring. Int J Mol Sci 2017;18.

35. Monthe-Dreze C, Rifas-Shiman SL, Gold DR, Oken E, Sen S. Maternal obesity and offspring cognition: the role of inflammation. Pediatr Res 2019;85:799-806.

36. Ditto B, Seguin JR, Tremblay RE. Neuropsychological characteristics of adolescent boys differing in risk for high blood pressure. Ann Behav Med 2006;31:231-237.

37. Ritchie K, Jaussent I, Stewart R, et al. Adverse childhood environment and late-life cognitive functioning. Int J Geriatr Psychiatry 2011;26:503-510.

38. Reuben A, Caspi A, Belsky DW, et al. Association of Childhood Blood Lead Levels With Cognitive Function and Socioeconomic Status at Age 38 Years and With IQ Change and Socioeconomic Mobility Between Childhood and Adulthood. JAMA 2017;317:1244-1251.

39. Logue MW, Panizzon MS, Elman JA, et al. Use of an Alzheimer's disease polygenic risk score to identify mild cognitive impairment in adults in their 50s. Mol Psychiatry 2019;24:421-430.

40. Mormino EC, Sperling RA, Holmes AJ, et al. Polygenic risk of Alzheimer disease is associated with early- and late-life processes. Neurology 2016;87:481-488.

41. Axelrud LK, Santoro ML, Pine DS, et al. Polygenic Risk Score for Alzheimer's Disease: Implications for Memory Performance and Hippocampal Volumes in Early Life. Am J Psychiatry 2018;175:555-563.

42. Korologou-Linden R, Anderson E, Jones H, Davey Smith G, Howe L, Stergiakouli E. Polygenic risk scores for Alzheimer's disease, and academic achievement, cognitive and behavioural measures in children from the general population. International Journal of Epidemiology 2019.

43. Chaudhury S, Brookes KJ, Patel T, et al. Alzheimer's disease polygenic risk score as a predictor of conversion from mild-cognitive impairment. Transl Psychiatry 2019;9:154.

44. Desikan RS, Fan CC, Wang Y, et al. Genetic assessment of age-associated Alzheimer disease risk: Development and validation of a polygenic hazard score. PLoS Med 2017;14:e1002258.

Figure 1. Flow-chart of the study population

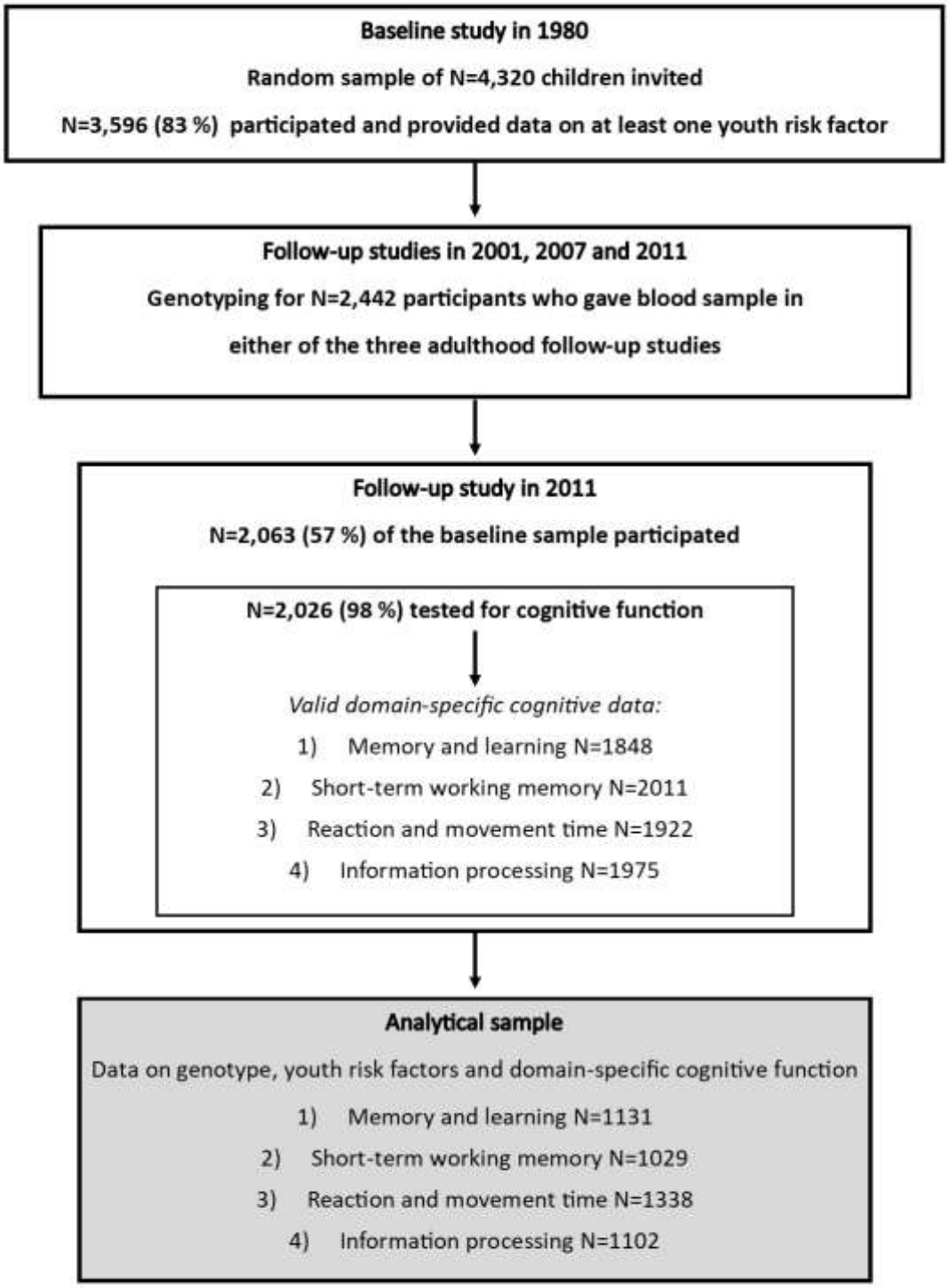


Table 1. Domain-specific multivariable models of youth factors and polygenic risk score with adulthood cognitive function[a]

	Memory and learning (PAL-test; N=1131)			**Short-term working memory (SWM-test; N=1029)**			**Reaction time (RTI-test; N=1338)**			**Information processing (RVP-test; N=1102)**		
	β	***p-value***	***95% CI***	***β***	***p-value***	***95% CI***	***β***	***p-value***	***95% CI***	***β***	***p-value***	***95% CI***
Polygenic risk score [b]	**-0.183**	**<0.001**	**-0.238 to -0.129**	**-0.103**	**0.001**	**-0.163 to -0.044**				**-0.174**	**<0.001**	**-0.229 to -0.119**
Youth variables												
Age [b]	**-0.198**	**<0.001**	**-0.265 to -0.132**	**-0.195**	**<0.001**	**-0.258 to -0.131**	-0.045	0.112	-0.102 to 0.011	-0.057	0.092	-0.124 to 0.009
Male sex	0.002	0.977	-0.112 to 0.116	**0.422**	**<0.001**	**0.298 to 0.546**	**0.402**	**<0.001**	**0.290 to 0.515**	**0.249**	**<0.001**	**0.135 to 0.362**
Systolic blood pressure [b]	**-0.072**	**0.033**	**-0.139 to -0.006**									
Physical activity [c]							**0.080**	**0.004**	**0.026 to 0.134**			
Birth weight [b]				**0.067**	**0.031**	**0.006 to 0.128**						
School performance [b]	**0.159**	**<0.001**	**0.099 to 0.219**	**0.085**	**0.010**	**0.020 to 0.151**	**0.111**	**<0.001**	**0.055 to 0.167**	**0.218**	**<0.001**	**0.159 to 0.278**
Maternal body mass index [b]	**-0.063**	**0.033**	**-0.122 to -0.005**									
Paternal myocardial infarction	**-0.445**	**0.027**	**-0.839 to -0.052**				**-0.449**	**0.008**	**-0.871 to -0.128**	**-0.411**	**0.029**	**-0.780 to -0.043**
Paternal stroke				**-0.816**	**0.025**	**-1.528 to -0.105**						
Socioeconomic status [b]										**-0.096**	**0.001**	**-0.155 to -0.038**
Adjusted R-squared (%)	**13.4**			**9.5**			**6.1**			**12.6**		

Estimates are presented domain-specifically for those variables that were associated ($p<0.1$) with cognitive function in the age and sex adjusted analyses. All domain-specific variables were entered in the same statistical model. Beta coefficients represent one SD change in cognitive function components for one SD/level increase in the youth factors or polygenic risk score. Bold font indicates associations that were statistically significant ($p<0.05$) in the multivariable model separately for each cognitive domain. PAL, Paired Associates Learning test; SWM, Spatial Working Memory test; RTI, Reaction Time test; RVP, Rapid Visual Information test; CI, confidence interval.

[a] only $p<0.1$ from age and sex adjusted models (bolded in Table 1) were included in backward selection and variables were excluded one by one (start from the one with the largest p-value) until the least significant p-value was <0.05 (age and sex included as compulsory predictors).

[b] standardized.

[c] age-specific standardized.

Table 2. Adulthood Cognitive Function According to Youth Risk Profile or Genetic Risk Groups

Cognitive domain	**Youth risk profile**	**N**	**β (95% confidence interval)** [a]	**P value**
Memory and learning (*PAL-test*)	Favourable	246	Reference	
	Intermediate	722	**-0.249 (-0.386 to -0.112)**	<0.001
	Unfavourable	212	**-0.573 (-0.756 to -0.391)**	<0.001
Short-term working memory (*SWM-test*)	Favourable	249	Reference	
	Intermediate	716	-0.011 (-0.150 to 0.127)	0.872
	Unfavourable	224	**-0.296 (-0.471 to -0.120)**	0.001
Reaction time (*RTI-test*)	Favourable	249	Reference	
	Intermediate	707	**-0.195 (-0.339 to -0.052)**	0.008
	Unfavourable	224	**-0.374 (-0.554 to -0.195)**	<0.001
Information processing (*RVP-test*)	Favourable	269	Reference	
	Intermediate	791	**-0.311 (-0.441 to -0.181)**	<0.001
	Unfavourable	243	**-0.772 (-0.940 to -0.605)**	<0.001
	Genetic risk	**N**	**β (95% confidence interval)** [b]	**P value**
Memory and learning (PAL-test)	Low	252	Reference	
	Intermediate	703	**-0.189 (-0.323 to -0.054)**	0.006
	High	225	**-0.501 (-0.671 to -0.332)**	<0.001
Short-term working memory (SWM-test)	Low	253	Reference	
	Intermediate	707	**-0.162 (-0.299 to -0.024)**	0.021
	High	229	**-0.378 (-0.549 to -0.206)**	<0.001

Reaction time (RTI-test)	Low	255	Reference	
	Intermediate	704	0.040 (-0.101 to 0.181)	0.581
	High	221	-0.008 (-0.186 to 0.170)	0.933
Information processing (RVP-test)	Low	275	Reference	
	Intermediate	780	**-0.225 (-0.352 to -0.098)**	0.001
	High	248	**-0.456 (-0.617 to -0.296)**	<0.001

[a] Adjusted for age, sex and polygenic risk score.

[b] Adjusted for age, sex and youth risk profile score.

Bold denotes statistical significance, $p<0.05$

Table 3. Association of the youth risk factor profile and cognitive function within the levels of genetic risk.

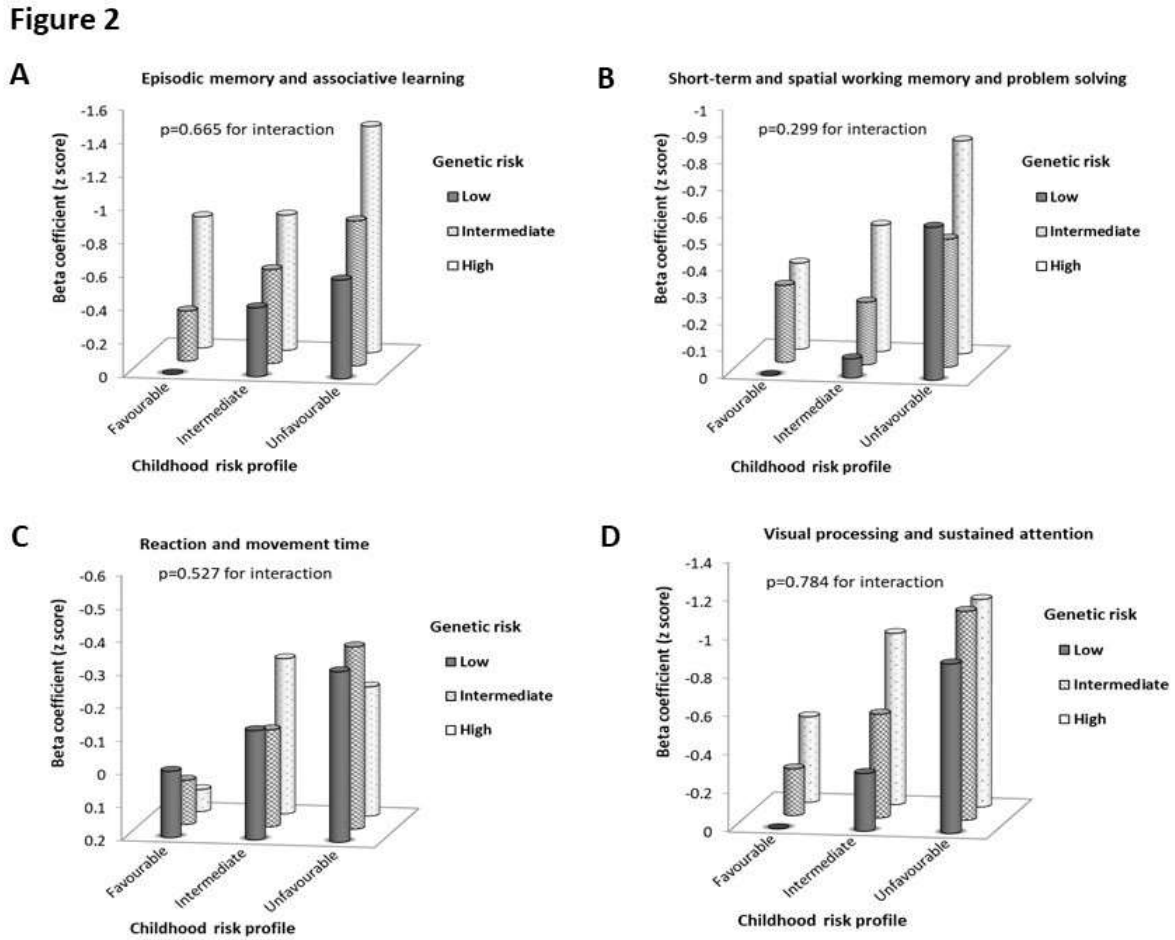
			Memory and learning (PAL-test)					**Short-term working memory (SWM-test)**					**Reaction time (RTI-test)**					**Information processing (RVP-test)**			
Genetic risk	Youth risk profile	N	β	p-value	95%CI		N	β	p-value	95%CI		N	β	p-value	95%CI		N	β	p-value	95%CI	
Low	Unfavourable	35	Reference				28	Reference				32	Reference				30	Reference			
	Intermediate	143	0.205	0.252	-0.147	0.558	144	**0.515**	**0.006**	**0.150**	**0.879**	152	0.198	0.320	-0.193	0.589	156	**0.590**	**0.001**	**0.254**	**0.926**
	Favourable	74	**0.630**	**0.002**	**0.238**	**1.021**	81	**0.589**	**0.003**	**0.200**	**0.978**	71	0.331	0.131	-0.099	0.761	89	**0.906**	**<0.001**	**0.549**	**1.263**
Intermediate	Unfavourable	137	Reference				147	Reference				140	Reference				157	Reference			
	Intermediate	427	**0.314**	**0.001**	**0.122**	**0.506**	429	**0.247**	**0.009**	**0.062**	**0.432**	427	**0.249**	**0.010**	**0.061**	**0.438**	475	**0.561**	**<0.001**	**0.381**	**0.741**
	Favourable	139	**0.573**	**<0.001**	**0.337**	**0.810**	131	0.187	0.112	-0.044	0.417	137	**0.416**	**<0.001**	**0.187**	**0.645**	148	**0.855**	**<0.001**	**0.634**	**1.077**
High	Unfavourable	40	Reference				49	Reference				52	Reference				56	Reference			
	Intermediate	152	**0.500**	**0.004**	**0.166**	**0.835**	143	0.298	0.068	-0.023	0.619	128	-0.061	0.712	-0.388	0.266	160	0.132	0.357	-0.150	0.414
	Favourable	33	**0.501**	**0.032**	**0.043**	**0.959**	37	**0.443**	**0.040**	**0.021**	**0.865**	41	0.328	0.119	-0.085	0.740	32	**0.565**	**0.006**	**0.165**	**0.966**

All analyses were adjusted for age and sex.

CI, confidence interval.

Bold denotes statistical significance, $p<0.05$.

Figure 2. Cognitive function according to youth risk factor profile and genetic risk. All analyses were adjusted for age and sex. The group with low genetic risk and favourable youth risk factor profile was used as the reference group.



Risk Factor Profile in Youth, Genetic Risk and Adulthood Cognitive Function: The Cardiovascular Risk in Young Finns Study

By Feitong Wu et al.

Supplemental material

Supplemental methods

Cognitive function

During the latest follow-up examination in 2011, the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK) was used to assess cognitive function among the participants aged 34-49 years, N=2,026. The CANTAB® is a computerized, predominantly nonlinguistic, and culturally neutral test focusing on a wide range of cognitive domains. The test is performed using a validated touchscreen computer system. The full test battery includes 24 individual tests from which a suitable test battery for each particular study may be selected. In the YFS, the test battery was selected so that it could be accomplished in 20–30 minutes and included tests that are sensitive to aging(1,2). The tests in YFS measured several cognitive domains: (a) short-term memory, (b) spatial working memory, (c) problem solving, (d) reaction time, (e) attention, (f) rapid visual processing, (g) visual memory, (h) episodic memory, and (i) visuospatial learning.

Cognitive testing was performed during clinical examination. Due to the blood sampling included in the study protocol, the subjects came to the examinations after fasting at least 12 hours. They were instructed to avoid smoking and heavy physical activity as well as to avoid

drinking alcohol and coffee during the previous evening and the morning before the examinations. Before the cognitive testing, the subjects were provided with a light snack, including a whole grain oat-based snack biscuit, a small portion of fruit or berry oatmeal, and weak fruit or berry juice.

During cognitive testing, the participants first conducted a motor screening test (MOT) measuring psychomotor speed and accuracy. In this study, the MOT was considered a training procedure where the participants were introduced to the equipment used in the testing and a screening tool to point out any difficulties in vision, movement, comprehension, or ability to follow simple instructions. During the MOT, a series of red crosses were shown in different locations on the screen, and the participants were advised to touch, as quickly as possible, the center of the cross every time it appeared. **Paired Associates Learning (PAL) test** was used to assess visual and episodic memory as well as visuospatial associative learning, containing aspects of both delayed-response procedure and conditional learning. During the PAL-test, one, two, three, six, or eight patterns were displayed sequentially in boxes placed on the screen. After that, the patterns were presented in the center of the screen, and the participants were supposed to point to the box in which the particular pattern was previously seen. The test moves on to the next stage if all the patterns are placed to the right boxes. In the case of an incorrect response, all the patterns are redisplayed in their original locations and another recall phase is followed. The test terminated if the patterns were still incorrectly placed after 10 presentation and recall phases. **Spatial Working Memory (SWM) test** was used to measure ability to retain spatial information and to manipulate items stored in the working memory, problem solving, and the ability to conduct a self-organized search strategy. During this test, the participants were presented with randomly distributed colored boxes ranging in number from four to eight. After that, the participants were supposed to search for tokens hidden in the boxes. When a

token was found, it was supposed to be moved to fill an empty panel on the right-hand side of the screen. Once the token had been moved from the box, the participant had to recall that the computer would never hide a new token in a box that previously contained one; therefore, the participants were not supposed to revisit the same boxes again. **Reaction Time (RTI) test** assessed speed of response and movement on tasks where the stimulus was either predictable (simple location task) or unpredictable (five-choice location task). In the first part of this test, a large circle was presented in the center of the screen. The participant was supposed to press a button on a press pad until a small yellow spot appeared in the large circle. When the yellow spot appeared, the participant was supposed to touch the spot as soon as possible with the same hand that was pressing the button on the press pad. In the second part of the test, the same task was performed, except that in this part, five large circles were presented on the screen, and the small yellow spot could appear in any of the five circles. Again, the participant was supposed to touch, as soon as possible, the yellow spot with the hand pressing the button on the press pad. **Rapid Visual Information (RVP) test** was used to assess visual processing, recognition, and sustained attention. In this test, the participant was presented with a number sequence (e.g., 3, 5, 7) next to a large box where numbers appeared in a random order. Whenever the particular sequence was presented, the participant was supposed to press a button on a press pad. At the beginning, the participant was given visual cues (*i.e.* colored or underlined numbers) to help the participant recognize the particular sequence. When the test proceeded, the cues were removed. The validity of the test battery has been previously studied comparing the individual outcome variables derived from each test to traditional pen-and-paper tests. These comparisons have provided correlation coefficients ranging between 0.12 and 0.26 for the RVP test(3), between 0.47 and 0.69 for the PAL test(4-6), 0.80 for the RTI test(7), and between 0.16 and 0.28 for the SWM test(3). Additionally, the prior studies have reported good test-retest reliability for the test battery (correlation coefficients ranging between 0.71 and 0.89)(8,9).

Supplemental references

1. De Luca CR, Wood SJ, Anderson V, *et al.* Normative data from the CANTAB. I: development of executive function over the lifespan. *J Clin Exp Neuropsychol* 2003; 25: 242–54.

2. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* 1994; 5: 266–81.

3. Smith PJ, Need AC, Cirulli ET, Chiba-Falek O, Attix DK. A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with "traditional" neuropsychological testing instruments. *J Clin Exp Neuropsychol* 2013;35:319-328.

4. Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Computerized delayed matching to sample and paired associate performance in the early detection of dementia. *Appl Neuropsychology* 1995;2:72-78.

5. Kim C, Lee JY, Ha TH, *et al*. The usefulness of the Cambridge Neuropsychological Test Automated Battery (CANTAB) for assessing cognitive functions in the elderly: A pilot study. *J Korean Ger Soc*. 2009;13:69-78.

6. Torgersen J, Flaatten H, Engelsen BA, Gramstad A. Clinical validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian epilepsy population. *J Behav Brain Sci* 2012;2:108-116.

7. Sexton CE, McDermott L, Kalu UG, *et al*. Exploring the pattern and neuronal correlates of neuropsychological impairment in late-life depression. *Psych Med* 2012:42:1195-1202.

8. Gonçalves MM, Pinho MS, Simões MR. Effects of socio-demographic variables on performance on the Cambridge Neuropsychological Automated Test for the assessment of dementia and Portuguese norms for older adults living in retirement homes. *Clin Neuropsychol* 2016a;30:284-317.

9. Gonçalves MM, Pinho MS, Simões MR. Test–retest reliability analysis of the Cambridge neuropsychological automated tests for the assessment of dementia in older people living in retirement homes. *Appl Neuropsychology:Adult,* 2016b;*23:*251–263.

Supplemental Table 1. Youth characteristics of participants in the Cardiovascular Risk in Young Finns Study

Variables	**Participants (n=2025)**	**Non-participants (n=1571)**	**p-value**
Youth factors from participants			
Age (years)	10.8 (5.0)	9.9 (4.9)	<0.001
Male sex, n (%)	922 (45.5)	842 (53.6)	<0.001
BMI (kg/m^2)	18.0 (3.1)	17.7 (3.1)	0.008
Systolic blood pressure (mmHg)	112.8 (11.9)	112.2 (12.5)	0.15
Diastolic blood pressure (mmHg)	68.6 (9.4)	69.0 (9.8)	0.24
LDL cholesterol (mmol/L)	3.42 (0.82)	3.45 (0.86)	0.43
HDL cholesterol (mmol/L)	1.56 (0.31)	1.56 (0.31)	0.91
Triglycerides (mmol/L)	0.67 (0.31)	0.66 (0.32)	0.43
Total cholesterol (mmol/L)	5.29 (0.90)	5.30 (0.93)	0.56
Daily smoking (yes/no), n (%)	309 (15.5)	218 (14.3)	0.32
Alcohol use (yes/no), n (%)	1229 (61)	777 (50)	<0.001
Fruit intake, n (%) [b]	1596 (79)	1259 (81)	0.19
Vegetables intake, n (%) [b]	681 (34)	552 (36)	0.27
Physical activity [a]	0.003 (0.99)	-0.003 (1.01)	0.86
Insulin (mU/L)	9.86 (6.00)	9.20 (5.89)	0.001
CRP (mg/L)	1.03 (3.12)	0.97 (2.59)	0.66
Academic performance	7.77 (0.72)	7.66 (0.74)	<0.001
Birth weight (g)	3520 (545)	3495 (550)	0.22
Youth factors from parents			
Mother's BMI (kg/m^2)	24.0 (3.8)	24.0 (4.0)	0.89
Father's BMI (kg/m^2)	25.5 (3.0)	25.5 (3.2)	0.56
Maternal diabetes	18 (0.9)	18 (1.2)	0.42
Paternal diabetes	29 (1.6)	25 (1.9)	0.62
Maternal hypertension	107 (5.4)	85 (5.6)	0.82

Paternal hypertension	170 (9.6)	125 (9.4)	0.84
Maternal myocardial infarction	8 (0.4)	5 (0.3)	0.72
Paternal myocardial infarction	37 (2.1)	13 (1.0)	0.02
Maternal coronary heart disease	35 (1.8)	18 (1.2)	0.16
Paternal coronary heart disease	65 (3.7)	40 (3.0)	0.31
Maternal stroke	8 (0.4)	5 (0.3)	0.72
Paternal stroke	13 (0.7)	16 (1.2)	0.18
Socioeconomic status	0.02 (0.59)	0.07 (0.58)	0.008

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein.

[a] age-specific standardized.

[b] frequency more than once a week.

[c] either parent had alcohol use enough to feel intoxicated at least once per week.

Supplemental Table 2. Age and sex-adjusted associations of youth factors and polygenic risk score with midlife cognitive function components

	Episodic memory and associative learning (PAL-test; N=1848)				**Short-term and spatial working memory and problem solving (SWM-test; N=2011)**				**Reaction and movement speed and attention (RTI-test; N=1922)**				**Visual processing and sustained attention (RVP-test; N=1975)**			
Youth factors from participants	β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI	
Polygenic risk score [a]	**-0.173**	**<0.001**	**-0.219**	**-0.126**	**-0.125**	**<0.001**	**-0.170**	**-0.080**	-0.003	0.915	-0.051	0.046	**-0.199**	**<0.001**	**-0.245**	**-0.153**
Age [a]	**-0.259**	**<0.001**	**-0.303**	**-0.216**	**-0.224**	**<0.001**	**-0.266**	**-0.182**	**-0.076**	**0.001**	**-0.120**	**-0.031**	**-0.114**	**<0.001**	**-0.158**	**-0.071**
Male sex	**-0.110**	**0.014**	**-0.199**	**-0.022**	**0.350**	**<0.001**	**0.266**	**0.434**	**0.401**	**<0.001**	**0.311**	**0.491**	**0.130**	**0.004**	**0.042**	**0.218**
Body mass index [a]	-0.020	0.525	-0.080	0.041	0.036	0.213	-0.021	0.094	0.004	0.907	-0.058	0.065	-0.042	0.171	-0.102	0.018
Systolic blood pressure [a]	**-0.074**	**0.006**	**-0.126**	**-0.022**	0.011	0.663	-0.039	0.062	0.014	0.612	-0.040	0.067	0.014	0.599	-0.039	0.067
Diastolic blood pressure [a]	-0.035	0.167	-0.085	0.015	0.004	0.857	-0.043	0.051	0.005	0.850	-0.046	0.056	**-0.048**	**0.055**	**-0.096**	**0.001**
Low-density lipoprotein cholesterol [a]	-0.023	0.328	-0.069	0.023	-0.023	0.298	-0.067	0.020	-0.012	0.620	-0.059	0.035	-0.003	0.887	-0.049	0.043
High-density lipoprotein cholesterol [a]	-0.015	0.501	-0.060	0.029	0.019	0.367	-0.023	0.062	0.014	0.536	-0.031	0.060	-0.004	0.861	-0.048	0.040
Triglycerides [a]	**-0.043**	**0.069**	**-0.089**	**0.003**	**-0.039**	**0.082**	**-0.082**	**0.005**	-0.024	0.309	-0.072	0.023	-0.022	0.350	-0.067	0.024
Total cholesterol [a]	-0.033	0.160	-0.078	0.013	-0.021	0.351	-0.064	0.023	-0.009	0.699	-0.056	0.037	-0.008	0.739	-0.053	0.038
Daily smoking (yes/no)	**-0.109**	**0.096**	**-0.237**	**0.019**	0.002	0.973	-0.120	0.124	-0.005	0.943	-0.135	0.126	-0.058	0.369	-0.186	0.069
Alcohol use (yes/no)	-0.055	0.389	-0.179	0.070	0.090	0.135	-0.028	0.208	0.014	0.834	-0.114	0.141	0.066	0.289	-0.056	0.189
Fruit intake weekly [b]	0.021	0.720	-0.092	0.134	0.056	0.302	-0.050	0.163	-0.023	0.694	-0.139	0.092	**0.154**	**0.006**	**0.043**	**0.265**
Vegetables intake weekly [b]	**0.081**	**0.090**	**-0.013**	**0.174**	-0.052	0.258	-0.142	0.038	0.039	0.421	-0.056	0.135	0.034	0.477	-0.060	0.128
Physical activity [c]	-0.012	0.609	-0.058	0.034	0.006	0.776	-0.038	0.051	**0.100**	**<0.001**	**0.053**	**0.147**	0.017	0.468	-0.029	0.063
Insulin [a]	**-0.054**	**0.044**	**-0.106**	**-0.001**	0.010	0.687	-0.040	0.060	-0.030	0.271	-0.084	0.024	**-0.051**	**0.057**	**-0.104**	**0.002**

C-reactive protein [a]	-0.039	0.104	-0.085	0.008	**-0.038**	**0.090**	**-0.082**	**0.006**	0.022	0.361	-0.025	0.069	-0.025	0.281	-0.071	0.021
Academic performance [a]	**0.190**	**<0.001**	**0.140**	**0.239**	**0.122**	**<0.001**	**0.075**	**0.169**	**0.109**	**<0.001**	**0.058**	**0.159**	**0.296**	**<0.001**	**0.248**	**0.343**
Birth weight [a]	0.020	0.405	-0.028	0.068	**0.070**	**0.003**	**0.025**	**0.116**	0.031	0.210	-0.018	0.080	0.035	0.157	-0.013	0.083
Youth factors from parents																
Maternal body mass index [a]	**-0.075**	**0.002**	**-0.123**	**-0.028**	-0.010	0.656	-0.055	0.035	-0.028	0.258	-0.076	0.020	**-0.116**	**<0.001**	**-0.162**	**-0.070**
Paternal body mass index [a]	**-0.052**	**0.036**	**-0.101**	**-0.003**	-0.016	0.505	-0.063	0.031	-0.020	0.428	-0.069	0.029	**-0.063**	**0.010**	**-0.111**	**-0.015**
Maternal diabetes (yes/no)	0.294	0.198	-0.154	0.743	-0.106	0.640	-0.551	0.339	**-0.439**	**0.058**	**-0.892**	**0.015**	-0.165	0.482	-0.625	0.295
Paternal diabetes (yes/no)	-0.084	0.662	-0.458	0.291	-0.034	0.851	-0.387	0.319	0.176	0.362	-0.202	0.554	-0.244	0.185	-0.604	0.117
Maternal hypertension (yes/no)	-0.022	0.830	-0.222	0.178	0.019	0.841	-0.169	0.208	-0.022	0.833	-0.226	0.182	0.048	0.633	-0.148	0.243
Paternal hypertension (yes/no)	**-0.236**	**0.004**	**-0.398**	**-0.073**	-0.081	0.302	-0.234	0.073	-0.061	0.469	-0.226	0.104	-0.118	0.147	-0.277	0.042
Maternal myocardial infarction (yes/no)	-0.188	0.606	-0.905	0.528	-0.063	0.853	-0.728	0.603	-0.457	0.217	-1.181	0.268	-0.451	0.199	-1.138	0.237
Paternal myocardial infarction (yes/no)	**-0.437**	**0.009**	**-0.766**	**-0.109**	-0.221	0.173	-0.539	0.097	**-0.394**	**0.022**	**-0.730**	**-0.058**	**-0.415**	**0.013**	**-0.744**	**-0.086**
Maternal coronary heart disease (yes/no)	-0.229	0.193	-0.573	0.115	-0.212	0.197	-0.534	0.110	-0.156	0.379	-0.505	0.192	**-0.285**	**0.093**	**-0.618**	**0.048**
Paternal coronary heart disease (yes/no)	-0.207	0.115	-0.464	0.051	**-0.239**	**0.055**	**-0.483**	**0.005**	-0.142	0.292	-0.407	0.122	**-0.232**	**0.070**	**-0.483**	**0.019**
Maternal stroke (yes/no)	-0.247	0.499	-0.966	0.471	**-0.732**	**0.031**	**-1.399**	**-0.066**	0.212	0.568	-0.515	0.939	-0.053	0.880	-0.742	0.636
Paternal stroke (yes/no)	-0.395	0.141	-0.922	0.131	**-0.784**	**0.003**	**-1.307**	**-0.260**	0.011	0.969	-0.521	0.543	-0.244	0.371	-0.780	0.291
Socioeconomic status [a]	**-0.120**	**<0.001**	**-0.164**	**-0.076**	-0.028	0.191	-0.071	0.014	**-0.090**	**<0.001**	**-0.135**	**-0.045**	**-0.213**	**<0.001**	**-0.256**	**-0.169**

Bold denotes p<0.1. All analyses adjusted for age and sex. CI, confidence interval.

[a] standardized. [b] frequency more than once a week. [c] age-specific standardized.

Supplemental Table 3. Adulthood Cognitive Function According to Youth Risk Profile Quartile Groups

Cognitive domain	**Youth risk profile**	**N**	**β (95% confidence interval)** [a]	**P value**
Memory and learning (*PAL-test*)	Q1 (Favourable)	310	Reference	
	Q2	298	-0.134 (-0.282 to 0.014)	0.075
	Q3	305	**-0.375 (-0.426 to -0.224)**	<0.001
	Q4 (Unfavourable)	267	**-0.512 (-0.675 to -0.348)**	<0.001
Short-term working memory (*SWM-test*)	Q1 (Favourable)	306	Reference	
	Q2	319	-0.014 (-0.165 to 0.137)	0.856
	Q3	287	-0.053 (-0.208 to 0.103)	0.506
	Q4 (Unfavourable)	277	**-0.283 (-0.442 to -0.124)**	<0.001
Reaction time (*RTI-test*)	Q1 (Favourable)	305	Reference	
	Q2	294	-0.113 (-0.271 to 0.046)	0.163
	Q3	300	**-0.185 (-0.342 to -0.027)**	0.021
	Q4 (Unfavourable)	281	**-0.355 (-0.516 to -0.194)**	<0.001
Information processing (*RVP-test*)	Q1 (Favourable)	339	Reference	
	Q2	327	**-0.194 (-0.334 to -0.054)**	0.007
	Q3	318	**-0.397 (-0.539 to -0.254)**	<0.001
	Q4 (Unfavourable)	319	**-0.755 (-0.904 to -0.607)**	<0.001

[a] Adjusted for age, sex and polygenic risk score.

Bold denotes statistical significance, $p<0.05$

Supplemental Table 4. Adulthood Cognitive Function According to Youth Risk Profile Quintile Groups

Cognitive domain	Youth risk profile	N	β (95% confidence interval) [a]	P value
Memory and learning (*PAL-test*)	Q1 (Favourable)	246	Reference	
	Q2	245	-0.116 (-0.280 to 0.048)	0.166
	Q3	231	**-0.296 (-0.464 to -0.128)**	0.001
	Q4	245	**-0.362 (-0.532 to -0.192)**	<0.001
	Q5 (Unfavourable)	212	**-0.592 (-0.774 to -0.409)**	<0.001
Short-term working memory (*SWM-test*)	Q1 (Favourable)	249	Reference	
	Q2	243	0.018 (-0.151 to 0.186)	0.835
	Q3	245	0.096 (-0.073 to 0.265)	0.264
	Q4	228	-0.160 (-0.333 to 0.012)	0.069
	Q5 (Unfavourable)	224	**-0.300 (-0.476 to -0.125)**	0.001
Reaction time (*RTI-test*)	Q1 (Favourable)	249	Reference	
	Q2	240	-0.122 (-0.298 to 0.053)	0.172
	Q3	239	**-0.219 (-0.395 to -0.044)**	0.014
	Q4	228	**-0.247 (-0.424 to -0.069)**	0.006
	Q5 (Unfavourable)	224	**-0.375 (-0.555 to -0.196)**	<0.001
Information processing (*RVP-test*)	Q1 (Favourable)	269	Reference	
	Q2	273	-0.139 (-0.295 to 0.018)	0.082
	Q3	253	**-0.328 (-0.487 to -0.170)**	<0.001
	Q4	265	**-0.487 (-0.647 to -0.327)**	<0.001
	Q5 (Unfavourable)	243	**-0.792 (-0.959 to -0.626)**	<0.001

[a] Adjusted for age, sex and polygenic risk score.

Bold denotes statistical significance, p<0.05

Supplemental Table 5. Cognitive function according to youth risk profile and genetic risk

		Episodic memory and associative learning (PAL-test)					Short-term and spatial working memory and problem solving (SWM-test)					Reaction and movement time (RTI-test)					Visual processing and sustained attention (RVP-test)			
Subgroups	N	β	p-value	95%CI		N	β	p-value	95%CI		N	β	p-value	95%CI		N	β	p-value	95%CI	
Low genetic risk																				
Favourable youth risk	74	Ref.				81	Ref.				71	Ref.				89	Ref.			
Intermediate youth risk	143	**-0.412**	**0.002**	**-0.675**	**-0.149**	144	-0.071	0.592	-0.331	0.189	152	-0.130	0.358	-0.407	0.148	156	**-0.300**	**0.015**	**-0.542**	**-0.057**
Unfavourable youth risk	35	**-0.592**	**0.002**	**-0.974**	**-0.210**	28	**-0.570**	**0.007**	**-0.981**	**-0.160**	32	-0.315	0.134	-0.726	0.097	30	**-0.881**	**<0.001**	**-1.266**	**-0.496**
Intermediate genetic risk																				
Favourable youth risk	139	**-0.300**	**0.025**	**-0.563**	**-0.037**	131	**-0.288**	**0.033**	**-0.552**	**-0.023**	137	0.066	0.644	-0.216	0.348	148	-0.242	0.051	-0.486	0.001
Intermediate youth risk	427	**-0.562**	**<0.001**	**-0.793**	**-0.330**	429	**-0.233**	**0.044**	**-0.460**	**-0.006**	427	-0.093	0.463	-0.341	0.155	475	**-0.539**	**<0.001**	**-0.750**	**-0.329**
Unfavourable youth risk	137	**-0.867**	**<0.001**	**-1.138**	**-0.597**	147	**-0.477**	**<0.001**	**-0.737**	**-0.217**	140	**-0.351**	**0.015**	**-0.632**	**-0.069**	157	**-1.086**	**<0.001**	**-1.330**	**-0.842**
High genetic risk																				
Favourable youth risk	33	**-0.786**	**<0.001**	**-1.170**	**-0.402**	37	-0.321	0.090	-0.692	0.051	41	0.134	0.487	-0.244	0.512	32	**-0.444**	**0.020**	**-0.819**	**-0.070**
Intermediate youth risk	152	**-0.810**	**<0.001**	**-1.070**	**-0.550**	143	**-0.471**	**<0.001**	**-0.731**	**-0.210**	128	-0.269	0.066	-0.555	0.017	160	**-0.890**	**<0.001**	**-1.131**	**-0.649**
Unfavourable youth risk	40	**-1.355**	**<0.001**	**-1.716**	**-0.994**	49	**-0.794**	**<0.001**	**-1.132**	**-0.456**	52	-0.190	0.289	-0.542	0.161	56	**-1.079**	**<0.001**	**-1.390**	**-0.768**

Adjusted for age and sex.
CI, confidence interval.
Bold denotes statistical significance, p<0.05