Conference on Epidemiological Birth Cohort Studies
Paula Rantakallio Memorial Symposium

12th – 13th June 2014
University of Oulu – Finland

C.L.C.E.
Centre For Life-Course Epidemiology

Northern Finland Birth Cohorts
1966 – 1986
Paula Rantakallio
(1930–2012)

Dedicated to the memory of Professor Paula Rantakallio
Welcome Greetings

Dear Colleagues,

On behalf of the organizing committee, it is my pleasure to welcome you to Oulu to participate in the Conference on Epidemiological Birth Cohort Studies (12-13th June 2014), dedicated to the memory of Professor Paula Rantakallio. Professor Paula Rantakallio was a pioneer in Epidemiological Birth Cohort Studies. Due to her efforts we are able to use data from the Northern Finland Birth Cohorts.

We are very grateful to all of the speakers whose presentations will describe the broad spectrum of excellent research performed in the NFBC and other birth cohorts all over world. We also wish to acknowledge all researchers who contributed to our abstract book which further illustrates the wide variety of ongoing NFBC research.

We hope the conference will be memorable and that you will all participate in the Dinner on Thursday 12th June 2014 in Restaurant Rauhala. Let’s have fruitful discussions during the conference and during the dinner! Also we hope you enjoy the midnight sun!

Olette lämpimästi tervetulleita!

On behalf of the organizing committee,

Juha Veijola, Chair

Organizing committee:

Marjo-Riitta Järvelin
Minna Männikkö
Saranya Palaniswamy
Anja Taanila
Juha Veijola
Tuula Ylitalo
The Pioneer for Public Health Science in Northern Finland

Professor Paula Rantakallio (1930-2012) graduated from the Medical school in 1957 and completed her specialization in pediatrics in 1965. She acted as a Professor in Public Health Sciences between 1987 and 1996 at the Department of Public Health Science and General Practice (current Institute of Health Sciences), University of Oulu.

In her work as a pediatrician in Oulu, Professor Rantakallio observed many shortcomings in the health of both mothers and children. Even though there was a clear reduction in infant mortality rates in Finland, the rates were still far from satisfactory. Therefore there was a great need for local research knowledge to improve public health care. Professor Rantakallio can be reckoned as a pioneer for public health science in Northern Finland, as in the 1960s the northern provinces of Finland were still a development area regarding public health science.

In the beginning of her career Professor Rantakallio worked as a researcher in Manchester and she defended her thesis in 1969. Her research goal was to develop methods that enable the identification of risk pregnancies as early as possible to prevent further problems in health. The value of such preventive studies has been recognized only recently as research increasingly shows the importance of the prenatal period and early childhood development to subsequent morbidity and well-being.

This was the starting point for health research of children born in 1966 in Northern Finland (Northern Finland Birth Cohort 1966, NFBC 1966). The work started during early pregnancy and is still ongoing with the study subjects having reached 48 years of age. In 1980’s a new birth cohort study (NFBC 1986) was initiated for children born in 1985-1986. The new study group collected twenty years later from the same area and using the same methods enables cross comparison of the data collected, and provides an opportunity to explore both individual and social changes that have occurred at the level of citizens' health and well-being.

The NFBCs represent a huge collection of data from early pregnancy until middle age. This unique database offers an unparalleled opportunity to study socio-demographic, environmental, developmental, metabolic, genetic and epigenetic determinants of disorders, diseases and especially their intermediate stages. These
research areas have a great importance due to their high public health impact and these conditions could be targets for health promotion.

The Northern Finland Birth Cohort Studies (NFBC 1966 and NFBC 1986) that Professor Rantakallio started have produced more than one thousand publications. Thanks to her pioneering work, hundreds of scientists around the world have been able to use the data in their research.

**Professor Marjo-Riitta Järvelin**

Institute of Health Sciences and Biocenter Oulu, University of Oulu, Unit of Primary Care, Oulu, University Hospital, Finland

Imperial College London, UK

**Professor Sirkka Keinänen-Kiukaanniemi**

Institute of Health Sciences, University of Oulu, Unit of Primary Care, Oulu University Hospital, Finland

**Professor Anja Taanila**

Institute of Health Sciences, University of Oulu, Unit of Primary Care, Oulu University Hospital, Finland
CONFERENCE ON EPIDEMIOLOGICAL BIRTH COHORT STUDIES
DEDICATED TO THE MEMORY OF PROFESSOR PAULA RANTAKALLIO

Day Thursday 12 – Friday 13 June, 2014
Place Kastelli Research Center, Auditorium, Aapistie 1, Oulu, Finland

PROGRAMME

DAY 1: JUNE 12, 2014

SESSION I:
Chair: Juha Veijola, University of Oulu

08.30 – 09.00 Coffee

09.00 – 09.15 Opening remarks
Kyösti Oikarinen, Dean of the Medical Faculty, University of Oulu

09.15 – 09.45 A New Dawn for Longitudinal Studies
Marjo-Riitta Järvelin, University of Oulu, Imperial College London

09.45 – 10.15 Contributions of Finnish Twin Cohort Studies to Understanding Use and Abuse of Alcohol
Richard J. Rose, Indiana University

10.15 – 10.45 Computational Medicine: a multidisciplinary and global endeavor to understand health and disease aetiology
Mika Ala-Korpela, University of Oulu & University of Bristol

10.45 – 11.15 Benefits of cohort studies for child and adolescent psychiatry
Irma Moilanen, University of Oulu

11.15 – 12.30 Lunch
SESSION II:

Chair: Marjo-Riitta Järvelin, University of Oulu, Imperial College London

12.30 – 13.00 Population Neuroscience of the adolescent brain
Tomas Paus, University of Toronto

13.00 – 13.30 Musculoskeletal research in NFBC
Jaro Karppinen, University of Oulu

13.30 – 14.00 From infancy to middle-age: a mental journey through NFBC 1966
Graham Murray, University of Cambridge

14.00 – 14.30 Coffee

14.30 – 15.00 Physical activity and fitness during the lifecourse
Tuija Tammelin, LIKES – Research center for Sport and Health Sciences

15.00 – 15.30 Prevalence and background factors of temporomandibular disorders
Kirsi Sipilä, University of Eastern Finland

15.30 – 16.00 Preterm birth and maternal pregnancy disorders as models to understand early origins of adult health and disease
Eero Kajantie, National Institute for Health and Welfare

18.00 Dinner at the Restaurant Rauhala, Mannenkatu 4, Oulu
DAY 2: JUNE 13, 2014

SESSION I:

Chair: Minna Männikkö, University of Oulu

08.45 – 09.15 Coffee

09.15 – 09.45 Polycystic Ovary Syndrome: what have we learned from the cohort studies. Laure Morin-Papunen, Oulu University Hospital

09.45 – 10.15 Using population isolates in disease genetics Aarno Palotie, Institute for Molecular Medicine Finland

10.15 – 10.45 Complex disease genetics: moving beyond GWAS to impact on population health Mark Daly, Harvard Medical School

10.45 – 11.15 Development of schizophrenia from a lifespan perspective within the Northern Finland 1966 Birth Cohort Study Matti Isohanni, University of Oulu

11.15 – 12.30 Lunch

SESSION II:

Chair: Marjo-Riitta Järvelin, University of Oulu, Imperial College London

12.30 – 13.00 Dispositional optimism in NFBC-1966, relations and antecedents Ellen Ek, University of Jyväskylä

13.00 – 13.30 Early adversity, epigemone and adolescent obesity Zdenka Pausova, University of Toronto

13.30 – 14.00 Design options in cohort studies: Sampling-based alternatives to a census of the study population Esa Läärå, University of Oulu

14.00 – 14.30 The Fetal Footprint Wayne Cutfield, University of Auckland

14.30 – 14.45 Closing words, Juha Veijola, University of Oulu
Speaker introductions

Professor Marjo-Riitta Järvelin graduated in Medicine and specialized in Pediatrics at the University of Oulu, Finland, has gained qualification in Medicine by General Medical Council, UK and is a Fellow in The Royal College of Physicians, FFPH. She has an MSc in Environmental Epidemiology and Policy from the University of London and PhD in Epidemiology and Medical Science from the University of Oulu, Finland. She is Professor and Chair in Lifecourse Epidemiology, affiliated at Imperial College London, UK, but holds a professorship at the Institute of Health Sciences at the University of Oulu, Finland and Consultancy at Oulu University Hospital, Finland. In 1991 she joined in the Northern Finland Birth Cohort (NFBC) Research Program; now as a Research Programme’s Scientific Director. She has been running large-scale population based studies for over 25 years, and been working on the genetic and early life environmental origins of multi-factorial diseases and disorders in close collaboration with many internationally well-known institutions, groups and networks. Consequently, over 400 researchers from all over the world are involved in these studies. Professor Järvelin has received funding from the Academy of Finland, University and University Hospital Oulu, Finland, MRC UK, Welcome Trust UK, the EU and NIH USA, among others. She has an active role in research training as a Director of Postgraduate Studies at School of Public Health, Imperial College London and as Honorary Pediatric and Public Health consultant, at Imperial College Healthcare NHS Trust. Professor Järvelin has published over 470 original papers, supervised 27 PhDs and many other postgraduate theses as well as examined 19 PhD theses. She has been honored by an Award of Excellence in Genetic Epidemiology at Imperial College London, in the UK, been awarded a title of the Epidemiologists of the year 2012 and a membership in The Academy of Science and Letters in 2013 in Finland.

Dr. Richard J. Rose is a Professor Emeritus at the Department of Psychological and Brain Sciences, Indiana University, United States (since 2000). He earned his PhD in psychology at the University of Minnesota in 1964. He has been working as a post-doctoral researcher in Montreal, Canada, in 1964-1965 and as an Assistant or Associate professor at the University of Illinois and Indiana University in 1965-1999. During 1980-1984 Professor Rose was a member or the Human Development Study Section, DRG, NIH (chair in 1981 and 1984), and since 1986 he was appointed as a Senior International Research Fellow, and in 1997 a Visiting Professor at University of Helsinki, Finland. Professor Rose has received many eminent awards such as the Dobzhansky Memorial Award for Lifetime Scholarship in Behavior Genetics (2007), Honorary Doctorate, Artis Psychologicae Honoris Cavsa, University of Jyväskylä, Finland (2009), and the IH/NIAAA R37MERIT Award (2000-2010).

Dr Mika Ala-Korpela is a Professor of Computational Medicine at the Institute of Health Sciences, University of Oulu, Finland and at the School of Social and Community Medicine, University of Bristol, UK. His research focuses on lipoprotein metabolism, development and applications of multi-parametric data analysis methods for metabolic phenotyping and risk assessment, and the use of various –omics technologies, particularly high-throughput serum NMR metabolomics, in clinical and epidemiological studies of common metabolic disorders. He has published around 130 articles in international peer-reviewed journals. Professor Ala-Korpela has more than two decades of experience in biomedical NMR spectroscopy and has pioneered high-throughput applications of NMR-
based metabolomics in molecular epidemiology and functional genetics. Under his lead Computational Medicine was selected as one of the strategic scientific areas for development and funding at the University of Oulu for 2012-2016. He is also a staff member in the UK Medical Research Council Integrative Epidemiology Unit (IEU) and is leading the related Metabolomics Core Facility at the University of Bristol. During the last ten years Professor Ala-Korpela’s team has focused on developing an NMR-based metabolomics platform for human serum and plasma. This novel methodology has now been used to analyze around 200,000 serum samples (in about 5 years). The methodology provides information on >200 metabolic measures with clear biochemical interpretation and significance. This platform has recently been applied in various large-scale epidemiological and genetic studies, the results of which have been published in the leading scientific journals. Several new NMR laboratories are currently being set up to apply the aforesaid serum metabolomics platform in large scale epidemiological and systems biology research; more and up-to-date information at http://computationalmedicine.fi.

Professor (emerita) Irma Moilanen is both a pediatrician and a child psychiatrist. Her main task was to chair the Clinic of Child Psychiatry both at the University of Oulu and the University Hospital of Oulu during the years 1984-2009, up to retiring. She began her scientific research by examining twins in different contexts: Those born in Oulu University Central Hospital 1965-73 (Thesis), those in Northern Finland Birth Cohorts (NFBC) 1966 and 1986, those in Finnish 1981 Nationwide Birth Cohort Study, The FIN-Twin project under leadership of professors Rose from Indiana University, USA and Kaprio from Helsinki and nowadays also attachment and development of twin infants. Research on Child Psychiatric Epidemiology has included mainly two big cohorts: Finnish 1981 Nationwide Birth Cohort Study, born in 1981, and Northern Finland Birth Cohorts (NFBC) 1966 and 1986, both including information on thousands of persons from pregnancy up to adulthood. Her main scientific interest has been in childhood development and neuropsychiatry, especially Autism Spectrum Disorders (ASD) and ADHD, studied in collaboration with USA: Harvard University, UCLA, University of Massachusetts Boston, Europe: University of Frankfurt, Germany, Karolinska Institute, Stockholm, Sweden, Cambridge University, UK, Africa Ain Shams University, Cairo, in addition to many domestic Universities. Membership in the EU-project on Early Autism (COST-ESSEA) has broadened knowledge and brought up more international collaboration. As an emerita, she is continuing research on mainly ASD and twins.

Professor Tomáš Paus is the Tanenbaum Chair in Population Neuroscience, Professor of Psychology and Psychiatry at the University of Toronto, and Senior Scientist at the Rotman Research Institute. He is an expert in mapping the human brain in health and disease using a variety of tools, including magnetic resonance imaging, positron emission tomography and transcranial magnetic stimulation. Over the past 10 years, Prof. Paus has initiated or joined several large-scale studies of brain maturation and cognitive development during adolescence, thus pioneering a new discipline of population neuroscience that operates at an intersection of epidemiology, genetics and neuroscience. In this work, he and his colleagues explore the interplay between genes and environment in shaping the human brain and, in turn, trajectories of mental and cognitive health. Professor Paus has published over 180 peer-reviewed articles, 13 book chapters, co-edited the Oxford Handbook of Transcranial Stimulation and wrote a book on Population Neuroscience. He received the Royal Society Wolfson Merit Award, Gold Medal of the Masaryk University, is an elected member of the International Neuropsychology Symposium and an elected fellow of the Association for
Psychological Science, serves as Associate Editor of the Human Brain Mapping and Social Neuroscience, and as a member of several Scientific Advisory Boards in Europe and North America.

**Dr Jaro Karppinen** graduated in Biochemistry in 1981, Licentiate in Medicine in 1989 and Specialist in Physical and Rehabilitation Medicine in 1997. Defended his doctoral thesis on treatment of sciatica in 2001 and became Docent in Physical and Rehabilitation Medicine in 2004. Since then has been part-time Professor of Physical and Rehabilitation Medicine. Additionally, he works at the Finnish Institute of Occupational Health. His research interests are mainly etiology (especially genetics), diagnostics and treatment of musculoskeletal disorders.

**Dr Graham Murray** trained in Physics and Philosophy at University of Oxford, Medicine at University of London, and psychiatry in Cambridge. He conducted postgraduate research training in Cambridge and University of Oulu, Finland, and graduated from his medical studies and PhD with distinctions. He was awarded competitive research fellowships from the UK National Institute of Health Research and Medical Research Council, and has won several research prizes, including from the European Psychiatric Association and Royal College of Psychiatrists. He is a University Lecturer at the Department of Psychiatry, University of Cambridge, a Principle Investigator in the University of Cambridge Behavioural and Clinical Neuroscience Institute, and an honorary consultant psychiatrist at the Cambridgeshire and Peterborough NHS Foundation Trust, where he also is the academic lead for acute psychiatry. Dr Murray utilizes fMRI, computational neuroscience techniques, pharmacological and neuropsychological methodologies to investigate the neural basis of specific neuropsychiatric symptoms, including delusions, hallucinations and anhedonia. He is also interested in cognitive functions in health and illness across the life course.

**Dr Tuija Tammelin** is working as a Research Director at LIKES – Research Center for Sport and Health Sciences, Jyväskylä, Finland (www.likes.fi/en). She is a specialist in exercise physiology and physical activity epidemiology with more than 70 international peer reviewed publications. She conducted her doctoral and post-doctoral studies in Oulu in Northern Finland Birth Cohort 1966 and 1986 studies. Nowadays her research interests include the determinants of physical activity and fitness during the lifecourse, the effects of physical activity and fitness on health and wellbeing, and the effectiveness of physical activity interventions in different populations.

**Professor Kirsi Sipilä** graduated in Dental Medicine in University of Oulu, Finland in 1986 and specialised in Clinical Dentistry (special competence in Prosthetic Dentistry and Stomatognathic Physiology) in the same university in 1994. She got PhD in University of Oulu in 2002. She joined in the Northern Finland Birth Cohort (NFBC) in 1997, and her thesis and later research has been mainly based on the NFBC. She has Docentships in Stomatognathic Physiology (University of Turku, 2009) and in Prosthetic Dentistry and Stomatognathic Pathology (University of Helsinki, 2013). She has acted as a Senior Lecturer from 1997 to 2009 and as a Senior Researcher from 2010-2012 at the Institute of Dentistry, University of Oulu. Currently she works as a Professor at the Unit of Dentistry, University of Eastern Finland, Kuopio, Finland and as a Senior Researcher (part-time) at Institute of Dentistry, University of Oulu, and as a Chief Dentist in Kuopio University Hospital, Finland. She holds Consultancy at Oulu University Hospital, Finland. Kirsi Sipilä’s main research interests are etiology, diagnosis and treatment of temporomandibular disorders.
(TMD), etiology and psychosocial background factors of facial pain as well as epidemiology of oral health. She has published 36 original papers and three chapters in textbooks, examined two PhD theses and currently supervises three PhD theses. She has supervised many postgraduate theses. She has been a visiting researcher in Tromso University, Norway, Imperial College, London, UK and Mahidol University, Bangkok, Thailand. She has been honoured by a Writer Award by the Finnish Dental Society Apollonia. She has received fundings from the Academy of Finland and Finnish Dental Society Apollonia.

**Dr Eero Kajantie** is an Academy Research Fellow at National Institute for Health and Welfare, Helsinki and Oulu, Finland. He is also affiliated as a Principal Investigator at Children’s Hospital, University of Helsinki, and holds a consultancy at Department of Obstetrics and Gynaecology, Oulu University Hospital. Dr Kajantie graduated as an MD in 1990 and started his research career after earning clinical qualification in pediatrics in 1998. After his 2003 PhD and a brief postdoctoral period at MRC Environmental Epidemiology Unit, Southampton, he combined research and clinical work earning additional clinical qualifications in clinical genetics (2006) and public health (2008). The main aim of Dr Kajantie's research is to gain insight to mechanisms that link conditions during fetal life and childhood with non-communicable and mental disorders in later life. His group has focused on preterm birth and maternal pregnancy disorders, such as gestational diabetes and hypertension in pregnancy, as models to understand these mechanisms. For this purpose he has established two studies utilising longitudinal cohorts of young adults, the Helsinki Study of Very Low Birth Weight Adults from 2003 onwards and, in collaboration with the Northern Finland Birth Cohort, the ESTER “Pregnancy, preterm birth and offspring health in adult life” from 2008 onwards. He also engages in extensive national and international collaboration within a multidisciplinary group of experts, including the Helsinki 1924-1944 Birth Cohort team. Dr Kajantie has published over 200 peer-reviewed original papers; his h index is 36.

**Dr Laure Morin-Papunen** specialized in Obstetrics and Gynecology in 1996 and in gynecologic endocrinology in 2000. She presented her thesis on the metabolic effects of metformin in polycystic ovary syndrome (PCOS) in 2000. Since, she has published over 40 international articles on polycystic ovary syndrome and endocrinology, focusing on the metabolic and reproductive disorders associated with the syndrome. She was also the project manager and researcher initiating the Finnish, RC multi-center trial: Effects of metformin treatment on infertility in PCOS women, “The METPLA study”. She is also the principal investigator in the PCOS-research group in the Northern Finnish Cohorts 86 and 66. She is working as an Assistant professor in the IVF and Gynecologic Endocrinology Unit in the University Hospital of Oulu, Finland. She is a fellow of the Finnish Endocrine Society and the actual President of the Finnish Society of Gynecology for Children and Adolescents (SLANGY).

**Professor Palotie** gained his M.D. and Ph.D. degrees at the University Of Oulu, Finland. He served his residency in laboratory medicine and earned his specialty in Clinical Chemistry (Clinical pathology) at the University of Helsinki. After his residency he founded and ran the diagnostic laboratory for molecular genetics at the Helsinki University Hospital and was Professor of Cell and Molecular Biology at the University of Helsinki. From 1998 to 2002 he was Professor of Pathology at the University Of California School Of Medicine, Los Angeles. From 2002 to 2008 he was Director of the Finnish Genome Center, an independent institute at the University of Helsinki. Since 2004 he has been a visiting Professor at the
Broad Institute of MIT and Harvard. He also holds a position at the Institute for Molecular Medicine Finland (FIMM) in Helsinki. From 2007 to 2013 Professor Palotie was a senior Group Leader at the Welcome Trust Sanger Institute in Cambridge, UK. Since 2013 he splits his time between the Finnish Institute for Molecular Medicine (FIMM) in Helsinki, The Broad Institute and Massachusetts General Hospital in Boston. Professor Palotie has a long history of research in genetics of Mendelian and complex traits. This has included locus and variant identification in monogenic diseases belonging to the Finnish disease heritage and linkage and association studies in complex traits. He investigates the genetic predisposition of traits affecting the Central Nervous System, particularly migraine, epilepsy, schizophrenia and autism. His work is based on using large, well-characterized special populations and family samples. Professor Palotie is also the co-chair of the neurodevelopmental arm of the UK10K project, which aims to sequence the exomes of 3000 schizophrenia and autism cases.

**Dr Mark Daly** is the founding chief of the Analytic and Translational Genetics Unit (ATGU) at Massachusetts General Hospital and an assistant professor in the Harvard Medical School. His research has historically focused on the development and application of statistical methods for the discovery and interpretation of genetic variation responsible for complex human disease and with the recent creation of the ATGU, he and other core faculty are now focused on the interpretation of genome sequence and the use of genome information in clinical settings. Mark is also a senior associate member and co-director of the Program in Medical and Population Genetics at the Broad Institute, where he leads many large scale genome sequencing studies in autism and inflammatory bowel disease. Daly’s group has developed numerous methods and widely used software tools, including GENEHUNTER and HAPLOVIEW, genetic analysis tools used in thousands of laboratories worldwide; GRAIL and DAPPLE, web-based utilities for the interpretation of genome-wide association results; and have contributed to additional widely distributed tools developed in the Broad community such as PLINK and GATK. His earlier work at the Whitehead Institute and Whitehead/MIT Center for Genome Research (precursor to the Broad Institute) was instrumental in developing an understanding of patterns of variation in the human and mouse genomes, and in the use of these patterns in disease gene mapping. While developing computational and statistical methods that can be broadly applied, his group has several primary medical genetics research foci. He has extensive research program in neuropsychiatric genetics - particularly in autism, schizophrenia and ADHD – and has led large-scale GWAS and exome sequencing efforts in this area. His lab serves as the analytic hub for the Psychiatric GWAS Consortium, and international consortium leading the largest collaborative GWAS studies in 5 major psychiatric disorders. He also has a longstanding effort in the mapping of genes for Crohn’s disease and ulcerative colitis where he helped found and lead an international effort that has identified more than 150 genetic risk factors and, in collaboration with Dr. Ramnik Xavier’s group, pursues the functional interpretation and clinical ramifications of these continued gene discovery efforts. More recently, the group also participates in numerous studies using exome sequencing to articulate the genetic origins of rare inherited diseases, early-onset and pediatric cancers, and severe adverse drug responses. Mark received his B.S. in physics from MIT and his Ph.D. in human genetics from Leiden University, Netherlands.

**Professor (emeritus) Matti Isomäki** of Psychiatry has acted as full professor of psychiatry 1994- 2013 at the University of Oulu, Department of Psychiatry. His scientific interests are focused on lifespan development of schizophrenia, Psychosocial and biological therapies of
psychoses, geriatric psychiatry, leadership, organization development and diagnostics in psychiatry. He has produced over 200 scientific articles. He has supervised about 20 doctoral thesis and awarded over 3 ME national and international funding. Professor Isohanni and his team have long experience in psychiatric epidemiology, long term follow-up studies, population based studies and brain imaging (both anatomy and function). Professor Isohanni has extensive domestic and international scientific networks. In detail he and his team have analysed the effects of psychiatric medications, particularly antipsychotics, on brain morphology, functioning and outcomes. This will be achieved utilising unique Northern Finland 1966 Birth Cohort samples that combine clinical and epidemiological measures and detailed assessments (genetics, epigenetics, neuroimaging, psychometric, register and clinical data). The team have made several clinically highly relevant scientific findings based on the Northern Finland 1966 Birth Cohort data. The diagnosis of schizophrenia is often delayed or conservative. Prevention of unwanted pregnancies may influence the incidence of schizophrenia. Brain volume alterations (mainly loss) and cognitive deviances exist in schizophrenia and may progress in midlife. Clinical and occupational outcomes in schizophrenia are not as good as they could be. Recovery is uncommon and educational and occupational outcomes unsatisfactory. Metabolic problems and altered lipid profiles begin in schizophrenia patients during their 30s but adverse clinical manifestations appear later; there exists a window for intervention to reduce cardiovascular related mortality. Excess mortality, primarily due to suicide, is a clinical reality in schizophrenia. Long duration of untreated psychosis (DUP) predicts poorer short-term but not long-term outcome; this result both supports and challenges early detection of psychoses.

**Dr Ellen Ek** is a licensed health psychologist, PhD (Psychology) and Adjacent Professor (Work and Health psychology) in University of Oulu. Her dissertation thesis dealt with psychosocial resources and well-being of young adults, and the developmental and social predictors of these resources. Her other research interests have been the dynamics of successful entrance into labour market, and early signs of marginalisation. She has also published on the relationship between psychosocial resources, especially dispositional optimism, and several aspects of health behaviour. Her future research interests lie in investigating psychosocial resources, their development and associations with well-being, taking into account the micro- and macro-environmental social context, especially work conditions and career pathways. She works as a private entrepreneur giving career, health and work psychological counselling and coaching, and as a post doc researcher in University of Jyväskylä.

**Dr Zdenka Pausova** obtained her MD degree from Purkyně University (Czech Republic) in 1986. She then received research training in Genetics at McGill University and the University of Montreal in Montreal, Canada (1990-1998). Currently Dr. Pausova is Senior Scientist in the Hospital for Sick Children and Associate Professor in the Departments of Physiology and Nutritional Sciences at the University of Toronto, Canada. Her research focuses on causes and health consequences of adolescent obesity. She co-directs the Saguenay Youth Study aimed at investigating cardiometabolic and brain health, and its genetic modifiers, in 1,000 Canadian adolescents and their parents (http://www.saguenay-youth-study.org). She has published 92 peer-reviewed papers and 3 book chapters. She received the Award for Excellence in Research from the Heart and Stroke Foundation of Canada, is an elected Fellow of the American Heart Association. Her main research areas are Obesity and cardio-metabolic disease in adolescence, Eating behavior, addiction and the adolescent brain and Induction of brown fat as a protection against diet-induced obesity.
Professor Esa Lääärä graduated from the Faculty of Social Sciences, University of Helsinki in 1981, obtained the degree of MSc in Applied Statistics at Oxford University in 1985, and the degree of Licentiate of Social Sciences at the University of Helsinki in 1987. Since 1981, he has worked in various research and teaching positions in the fields of statistics, biostatistics and epidemiology at the Finnish Cancer Registry as well as at the Medical Schools of the Universities of Kuopio, Tampere and Oulu. From 1991 onwards he has contributed to various studies and publications in the Northern Finland Birth Cohort (NFBC) Research Program. In 2000 he was appointed to permanent professorship at the Department of Mathematical Sciences of the University of Oulu. Since 2009 he is a visiting professor at the University of Tartu, Estonia, and has worked as a consultant for the Finnish Office of Health Technology Assessment and as an adviser for the International Agency for Research on Cancer. He was the chairperson of the Finnish Society of Biostatistics from 1997 to 1999 and the President of the Nordic Region of International Biometric Society from 2004 to 2008. Professor Lääärä has published over 120 peer-reviewed articles, supervised 6 PhD dissertations and over 40 MSc theses, and has been a pre-examiner or opponent of 13 PhD dissertations. He was awarded the title of “Epidemiologists of the Year” in 2009 by the Finnish Epidemiological Society.

Dr Wayne Cutfield is Professor of Pediatric Endocrinology in the University of Auckland and Director of the Liggins Institute. He established a Pediatric Endocrine Service in Starship Hospital, and was Director of the service for many years. He is Chairman of the NZ Growth Hormone Committee, and has been President of the Asia Pacific Pediatric Endocrine Society (APPES). He has international research expertise in three broad areas: assessment of insulin action in children, early life programming of metabolic disease, and evaluation and management of growth disorders in childhood. He has authored more than 120 peer-reviewed journal articles (which include publications in the New England Journal of Medicine and Lancet), more than a dozen book chapters, and has acquired 5 patents.
The Northern Finland Birth Cohort study programme (NFBC) is the product of a project initiated in the 1960s to examine risk factors involved in pre-term birth and intrauterine growth retardation, and the consequences of these early adverse outcomes on subsequent morbidity.

Pregnancies were followed prospectively from the first antenatal contact (10-16\textsuperscript{th} gestational week, at community health clinics) including complications and diseases such as infections, gestational diabetes and hypertension, which were further scrutinized from patient records, as was the neonatal outcome. Collection includes stored serum samples for NFBC1986 from 10-12\textsuperscript{th} gestational week.
The children were followed-up at the ages of 6-12 months, 7-8 years (y) (NFBC1986 only), 14-16y (NFBC1966, 1986), psychiatric and metabolic health subsamples at 22-26y (NFBC1986) and at the age of 31y and 46y (NFBC1966). Psychiatric subsamples were followed-up at 34 and 43y. At these time points, a wide range of phenotypic, lifestyle, demographic and other data were gathered using questionnaires and clinical examinations. Extensive prospectively collected growth data between birth and 16y are available.

The 16y (NFBC1986, up to n=6795), 31y (NFBC1966, n=6033) and 46y (NFBC1966, n=5951) clinical outcome data include blood pressure, pulse, ECG, ultrasound echocardiogram, carotis ultrasound, hearth rate variability and barofeflex measurements, anthropometry and body composition, cognitive tests, skin prick tests, lung function (spirometry), physical fitness and sleep measures, glucose tolerance test, detailed mental, eye, dental and musculoskeletal assessments, hearing in school age, blood samples including DNA, RNA, leukocyte telomere length (LTL), fasting glucose, insulin, lipids, selected hormones (e.g. testosterone, cortisol, SHBG, LH, FSH, TSH, T4), as well as metabonomic data and stored serum, plasma and cells. Genomewide genotype (GWAS) and LTL data is for up to 5755 in NFBC1966 (exome chip for 1500) and GWAS, metabochip, exome chip and LTL for 4000-5140 in NFBC1986. Psychiatric follow-up studies provide over 1,000 MRI brains scans at various ages in the NFBC1986 and NFBC1966.

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References for different areas of research and the NFBC data:


Northern Finland Birth Cohort 1966
46-year data collection

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The Northern Finland Birth Cohort 1966 data collection started at 1965, when all mothers in Northern Finland with expected date of birth in the year 1966 were required for the study (12 068 mothers, 12 231 children, 96.3\% of all births during 1966 in that area).

Information about family history, social relationships, environment, mother’s health habits and clinical parameters (hemoglobin, weight, blood pressure) were collected from antenatal clinics, hospital registers and by postal questionnaires.

Obstetric data was collected during the perinatal period in delivery hospitals and antenatal clinics (N = 11 924/ 12 231, 97.5\% retrieved).

Information on children’s growth, health and development was collected from children’s welfare clinics when the children were 1 year olds (N = 10 821 / 11 870, 91.2\%). Yearly growth information (weight and height) from 1 year to 16 years has been collected from children’s welfare.

Postal questionnaire at 14 years of age included items about growth, health, living habits, school performance and family situation (11 010 / 11 764, 93.6\%).

At the age of 31 years, both postal questionnaire and clinical health examination were performed. The former included items about social background, health related habits, sickness and symptoms (N = 8767 / 11322, 77\%). Clinical health examination was performed for those who lived in provinces of Oulu and Lapland or in Helsinki area (n=6033 / 8497, 71.3\%). The examination included measurement of blood pressure, weight, height, waist-hip ratio, physical performance (grip strength, back extensor muscle strength, step-test), skin allergy (prick-test), and spirometry. In addition, blood samples were taken and many hormones, cytokines and metabolic parameters markers have been analyzed. Also DNA was extracted from blood samples and genome-wide genotyping was performed for 324 000 single nucleotide polymorphisms (SNP) and about 70 000 CNVs (Copy number of variations using Illumina HumanCNV370 Duo Beadchip (“370K”). These data were statistically imputed up to 3 855 963 SNPs for 5402 individuals. In addition Infinium HumanExome BeadChip was used for more targeted genotyping in 1500 Subjects consisting of >250 000 markers for a range of common conditions, such as type 2 diabetes, cancer, metabolic and psychiatric disorders.
Between 4/2012 and 2/2014, at the age of 46 years, a large health examination was performed, including questionnaires, clinical examinations and collection of more than 250,000 biological samples. Two postal questionnaires were sent for all subjects whose addresses were known (N = 10,300, ~ 6,900 answered). During the clinical examinations, two additional questionnaires were filled and afterwards one questionnaire. Questionnaires included items about social background, workload and occupational health, economy, lifestyle habits (sleep, smoking, physical activity, and nutrition), medication, sickness, organ-specific symptoms (musculoskeletal, gastrointestinal, ophthalmological, dental, respiratory, neurological, dermal, and gynecological symptoms), psychiatric symptoms (depression and anxiety), personal traits, physical functioning, quality of life, use of health services, and family history of diseases.

Clinical examinations were performed with three teams (Oulu region, Northern Finland and Southern Finland) and with more than 30 field examiners. Basic clinical health examinations were done for the whole cohort (N = 59,51) including blood pressure, 15-lead digital ECG, weight, height, bioimpedance (Inbody 720), waist-hip circumferences, physical performance (4 min step-test, back muscle endurance strength test, grip strength test), hearth rate variability, thermal perception threshold and thermal pain tolerance test, pressure pain threshold and tolerance test, skin allergy test (prick test), spirometry, 2-hour oral glucose tolerance test (with 0, 30, 60, and 120 min sample collections), cognitive test with iPad, and 2-week accelerometer measurement (from wrist with Polar Active and hip with Hookie) with diary.

In addition, more extensive clinical examinations were performed for the Oulu population (1,950 of 3,150 subjects participated) including thermal perception threshold and tolerance test, dental examinations and dental 3D scanning, pulse wave measurement (central blood pressure), more extensive autonomic nervous system tests, heart (echo) and carotis ultrasound, radiography of knees, ankles, foost, and maxillofacial region, spinal and ankle movement tests, lower back movement control impairment tests, and sciatica-neurology tests.

Lumbar MRI will be done for this subpopulation before the end of 2014 (currently 1,200 subjects have been scanned) and ophthalmological examinations will be done for half of the whole population (randomly selected) before the end of 2014 (currently ~ 2,300 subjects have been examined).

Biological samples were taken from the whole population (blood, fecal, urine, salve and hair) and already 30 basic parameters form blood has been analyzed. During the next years, many additional
parameters will be analyzed (hormones, cytokines, immunoglobulins, metabolomics). DNA samples were also collected at 46 year of age enabling the epigenetic analyses and GWAS analysis for those who did not take part into 31-year study. Epigenetic analyses will be performed by analyzing the general methylation level with HumanMethylation450 BeadChip (Illumina) and the national Genome-wide methods infrastructure network of Biocenter Finland (http://www.biocenter.fi/) will be used. White blood cells and whole blood RNA samples have also been collected. Extraction and analyses will be performed within the next 5 years and some data will be available in future.

In addition, data has been collected from national registers until the end of 2012 (hospitalizations, medications, death causes, cancers, infectious diseases, disability pensions, employment and investments).
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The levels of toxic and essential elements in human blood in northern Finland and its health implications

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INTRODUCTION

Scientific risk assessment of chemicals is scientific evaluation of the probability of human health effects resulting from hazardous exposure. Biomonitoring, by e.g. analysing blood levels of compounds is an important tool for evaluating total exposure and internal dose of environmental contaminant for a more precise and realistic human health risk assessment.

From Northern Finland 1966 Birth Cohort (NFBC 1966) biobank, 250 blood samples (127 male and 123 female) were selected for the analysis of toxic and essential elements. The selection criteria were based on individual persons born and living the last 5 years in the Eastern or Western part of Lappland.

METHODS

Blood samples were investigated for concentrations of toxic elements such as mercury, arsenic, cadmium, lead, as well as essential elements such as manganese, copper, zinc, and selenium.

The aim of this study is to assess those elements in Lappish population, and to compare the results with European and other populations. In addition, it is the aim to compare the biomonitoring data with safety limits and health parameters.

RESULTS

The concentration of mercury ranged from 0.23 to 14.54 μg/L, with a median value of 2.06 μg/L. Arsenic level ranged from 0.15 to 18.02 μg/L, with a median value of 0.53 μg/L, cadmium level from 0.11 to 4.03 μg/L, with a median value of 0.49 and lead level from 2.06 to 145.5 μg/L, with a median value of 13.6 μg/L.

Two “toxicological” cut-off points were used. In the case of mercury 8.8%, of the studied population were higher than the average of the normal population values, while 21%, were higher than toxicological values established by international organizations.

The corresponding percentages for arsenic, cadmium and lead levels were 6.8%, 46%, and 1.6% higher values than in normal population, and 0%, 0% and 2%, higher than international reference values, respectively.

CONCLUSIONS

No differences neither between males and females, nor between Eastern and Western part of Lappland were observed.

As expected, significant correlations between mercury and fish consumption (correlation coefficient 0.424), as well between cadmium and smoking (0.368) were seen.
Computational medicine: a multidisciplinary and global endeavour to understand health and disease aetiology

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Comprehensive profiling of metabolites in blood specimens, also known as metabolomics, is increasingly used to gain insights into the molecular mechanisms of common diseases such as diabetes and heart disease (1). Detailed metabolic phenotyping, with absolute quantification of metabolites, also improve current methods for risk assessment of future disease onset. To realize this potential of NMR metabolomics on the population level, we have set up an automated high-throughput platform for human serum NMR metabolomics (2) that has been used to analyse around 200,000 samples from numerous epidemiological studies during the past 5 years. The methodology features quantification of >200 specific molecular identities in physiological units, including lipoprotein subclass profiling, fatty acid composition, and various small molecules such as amino acids and glycolysis precursors. These molecular data relate to multiple biological pathways and metabolic functions in health and disease, including the metabolic signatures of insulin resistance, obesity, and diabetes (3,4). This novel line of molecular epidemiology allows a more detailed molecular understanding of biochemical pathways and disease pathologies. Our results also demonstrate improved risk prediction for cardiovascular disease and all-cause mortality (5). Still, the analyses of quantitative NMR metabolomics data have only scratched the surface of applications in public health and disease prevention. The full benefits of the methodology will emerge once blood samples from many more large studies and clinical trials are profiled. The technological characteristics of the serum NMR metabolomics platform will be presented in relation to applications in epidemiology and genetics.

REFERENCES


Gene environment interaction analysis of obesity and asthma

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INTRODUCTION

Asthma and obesity are common diseases with considerable impact on public health. Prospective studies showed that obesity is a risk factor for developing asthma and a causal relation has been proposed. However, there is limited evidence for the existence of shared genetic effects and it is not yet clear how obesity and genetic factors jointly influence the risk of developing asthma.

We sought to determine whether obesity (body mass index of 30 or greater) modifies the risk of developing asthma and to assess whether there is evidence for a causal relation linking the genetic risk of developing obesity with asthma.

METHODS

The analyses were performed in genotyped individuals of two northern Finland birth cohorts. The discovery set (NFBC1966) and the \textit{in silico} replication set (NFBC1986) comprised a sample of 4182 and 1441 individuals. The presence of asthma was determined by self-report of a physician diagnosis of asthma, and body mass index (BMI) was measured at time of clinical examination (at 31 and 16 years old respectively). Sixty SNPs previously associated with asthma or obesity from the GWAS catalogue were analysed. The gene environment interactions were formally tested with a full interaction model using logistic regression. The significant interactions (P<0.05) found in the discovery dataset were meta-analysed with results of the replication set using fixed and random effects model.

RESULTS

We prioritized six significant (P<0.05) SNP interactions in the discovery set for replication (Fig. 1). Only one of the prioritized loci was previously associated with obesity (BMI). After meta-analysis with the replication set, we identified one directionally consistent interaction with obesity (P < 6.5x10\textsuperscript{-3}) in rs2786098 near DENND1B, a SNP previously associated with asthma (Fig. 2). After meta-analysis, we did not find significant or directionally consistent interactions in SNPs previously associated with BMI or Obesity.

CONCLUSIONS

Our limited dataset suggests that obesity modifies the genetic risk of developing asthma. We did not found evidence for the hypothesis that obesity causes asthma.
### Table 1: Six SNPs (out of sixty overlapping SNPs) had significant (P<0.05) gene x environment interactions in the discovery dataset (NFBC1966) and were prioritized for replication in the NFBC2006.

The model consists of the full interaction terms and adjustment terms for sex and the first six principal components besides. Entry line in bold denotes a SNP with a significant interaction. Abbreviations: OR, odds ratio; SE, standard error; P, p-value of the statistical test; N, number of paired genotype and phenotype samples; EA, effect allele; EAF, effect allele frequency.

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### Fig 2: Meta-analysis of the six SNPs (out of sixty overlapping SNPs) with significant (P<0.05) gene x environment interactions in the discovery dataset suggests that rs2786908 interacts with obesity to modify the risk of asthma. Abbreviations: OR, odds ratio; SE, standard error; P, p-value of the statistical test; N, number of meta-analysed individuals; P_{Het}, Cochran heterogeneity test; I^2, heterogeneity statistics.
Sex differences in microstructure of white matter tracts in a birth cohort sample of young adults

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INTRODUCTION
Sexual dimorphism of the brain is seen in differences in neural connectivity in white matter (WM)¹. A major motivation for studying brain sex differences arises from sex related vulnerabilities to developmental and psychiatric disorders.

Studies using diffusion tensor imaging (DTI) have recently shown mainly more coherent diffusion, as higher fractional anisotropy (FA), and lower myelin or higher axonal caliber, as lower magnetization transfer ratios (MTR), in male vs female WM².

In this study, two modalities of magnetic resonance imaging - DTI and magnetization transfer imaging (MTI) - were used to collect data for the analyses of WM tracts of 447 participants from the Northern Finland 1986 Birth Cohort (NFBC 1986).

METHODS
Of the 9259 cohort members, 1344 were invited and 468 (34.8%) participated in the field study. DTI, MTI and structural T1 images were produced of 189 male and 258 female participants.

Group comparisons were made between male and female DTI based white matter skeletons and MTR maps using a voxel-wise permutation method.

RESULTS
Male FA was shown to be significantly higher than female FA throughout the WM (p<0.01). Also the comparison of the MTR maps showed significantly higher male MTRs in most WM regions.

CONCLUSIONS
The results show large differences in comparison to most other studies, in the sense of high male vs female FA and MTR. One can argue that the finding arises from our relatively large sample.

REFERENCES
Smoking and use of antibiotics during pregnancy are risk factors for inflammatory bowel disease

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INTRODUCTION

The pathogenesis of inflammatory bowel disease (IBD) is unclear. Environmental factors in combination with genetic predisposition may play a role. The aim of this study was to analyse prenatal risk factors for IBD in a well described birth cohort from Northern Finland.

METHODS

The prospectively collected Northern Finland Birth Cohort 1966 (NFBC 1966) is a longitudinal research program to promote health and well-being of the population (http://www.oulu.fi/nfbc/). The population is comprised of mothers living in the two northernmost provinces of Finland, Oulu and Lapland with expected dates of delivery between Jan 1st - Dec 31st, 1966 (12068 mothers, 12231 children, 96.3% of all births during 1966 in that area). Information about family history, social relationships, environment, mother’s health habits and clinical parameters were collected from antenatal clinics, hospital registers and by postal questionnaires. Between years 2012 and 2014, at the age of 46 years, a large health examination was performed including both questionnaires and clinical examination, including questions about physician’s diagnosis of IBD. 6852 subjects (66%) answered for the postal questionnaires. Data were analyzed by chi square test, Fishers exact test and counting relative risks (RR).

RESULTS

Data were available from 6685 individuals, of whom 175 (2.6%) reported physician’s diagnosis of IBD, 88/2957 male and 87/3553 women. Maternal age, gestation age, gestation weight, maternal comorbidities, parity, number of siblings, household farm animals or pets, living in an urban area and social class were not associated with IBD of children until 46 years of age. However, consumption of antibiotics during pregnancy [(23/549 vs. 140/5375) RR 1.6 (1.0-2.4), p=0.041], smoking during pregnancy [continued, 37/892 RR 1.7 (1.2-2.5) vs. stopped, 8/406 RR 0.7 (0.4-1.5) vs. never smoked 128/5247 RR 0.7 (0.5-1.0), p=0.0033] and living in the most northern part of Finland [above the Arctic Circle 19/419 RR 1.7 (1.1-2.8) vs. southern Lapland 45/1943 RR 0.8 (0.6-1.1) vs. Oulu district 111/4148 RR 1.0 (0.7-1.3), p= 0.0188] were associated with IBD.

CONCLUSIONS

Smoking and consumption of antibiotics during pregnancy and mothers’ living above the Arctic Circle were risk factors for IBD until the age of 46.
Identification of novel factors associated with leukocyte telomere length in the NFBC1966

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INTRODUCTION

Telomeres are protective DNA-protein structures that cap the ends of linear chromosomes. In humans, longer mean leukocyte telomere length (LTL) is positively correlated with lifespan, while shorter LTL is associated with increased risk of age-related disease. We aim to identify genetic and other factors associated with LTL in the NFBC1966, in order to shed light on the processes underlying healthy ageing.

METHODS

Mean relative LTL measurements have been obtained for 5,620 participants, using genomic DNA samples prepared from blood taken at age 31. Consistent with other studies, we observe a gender difference, with women having a longer mean telomere length than men.

RESULTS

To date, we have identified novel associations between LTL and the body mass index (BMI) trajectory from early childhood to adulthood in women¹; with long-term unemployment in men²; and, in a collaborative study, with common genetic variants in seven loci³.

CONCLUSIONS

Further longitudinal studies are now required to elucidate the long-term effects of these and other factors on LTL, healthy ageing and disease risk, and to investigate the gender differences observed.

REFERENCES


Figure 1. Mean LTL in women is 4.8% longer than men in the NFBC1966 at 31y
Growth early infancy and adult fat distribution in a cohort prospectively followed from foetal period to adulthood: findings from the Northern Finland Birth Cohort 1966 study

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INTRODUCTION

Total adiposity, as measured by body mass index (BMI), and the relative distribution of abdominal to peripheral adiposity, as measured by waist-hip ratio, have been shown to be separate and independent risk factors for coronary heart disease. While studies suggest that increased postnatal growth rate may predispose infants to overweight and obesity later in life, its impact on adult body fat distribution is less clear. We examined the prospective relation of early growth and adult fat distribution in the 1966 Northern Finland Birth Cohort study.

METHODS

We analysed data of 4,987 men and women with prospectively collected data on weight at birth and at one year, as well as anthropometric measures and other clinical, health and lifestyle data at 31-year follow-up. We used waist-hip ratio as our indicator for the relative distribution of abdominal (waist circumference) to peripheral (hip circumference) fat.

RESULTS

Increasing weight gained from birth to one year was associated with increasing BMI at age 31 years (P for trend <0.001). Adjusting for birth weight, sex, adult BMI and other factors across the life course, weight gained from birth to one year was associated with increasing adult waist circumference by 1.4 (95% confidence interval [CI] 1.1 to 1.75) cm and hip circumference by 0.6 (95% CI 0.5 to 0.7) cm, but with decreasing waist-hip ratio by -0.004 (95% CI -0.006 to -0.002). Stratifying by birth weight and weight at 1 year, those who were both in the lower birth weight and weight gained at one year categories had smaller adult BMI, waist circumference and hip circumference, but had higher waist-hip ratio as compared to those who were in the both higher categories of weight at birth and at one year.
CONCLUSIONS

Early postnatal growth is related to increasing adiposity in adulthood but, for a given body size achieved in adulthood, it is associated with decreasing abdominal fat relative to peripheral fat. Increased postnatal growth, at least during early infancy, may promote a favorable adiposity phenotype later in life.
Serum sex hormone-binding globulin and testosterone in relation to cardiovascular disease risk factors in young men: a population-based study

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INTRODUCTION

Reduced sex hormone-binding globulin (SHBG) concentration predicts insulin resistance and type 2 diabetes, but its association with cardiovascular disease (CVD) risk is unclear. We examined the association between SHBG and cardiovascular risk factors, independently of total testosterone (TT), in young men.

METHODS

This is an observational, cross-sectional study of 2716 men aged 31 participating in the Northern Finland Birth Cohort Study 1966 who were clinically examined and
provided fasting blood samples. The exposure variables were sex hormone-binding globulin (SHBG) and total testosterone (TT), and the outcome variables were blood pressure (BP), lipids, and C-reactive protein (CRP) as biological CVD risk markers.

RESULTS

SHBG concentration was significantly and inversely related to systolic and diastolic BP, triglycerides and CRP, but positively to HDL cholesterol after adjusting for insulin, BMI, waist circumference, smoking, education and physical activity (all P<0.05). These linearly graded associations persisted with additional adjustment for TT. SHBG was significantly associated with total cholesterol only with adjustment for covariates and TT (P<0.05). The direction and magnitude of associations between TT and risk factors were variable, but further adjustment for insulin, adiposity and SHBG showed positive associations between TT and BP, total and LDL-cholesterol and triglycerides and an inverse association with CRP (all P<0.05), but its relation with HDL-cholesterol was no longer significant.

CONCLUSIONS

In this cohort of young adult men, increasing SHBG concentration was associated with a more favourable CVD risk profile, independently of TT. SHBG concentration modified the associations of TT with CVD risk factors.

REFERENCES

Genome-wide association study in 8,997 women, identifies genetic variants at five genomic loci associated with stress and urgency urinary incontinence

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INTRODUCTION

Both twin and family studies have provided convincing evidence for genetic predisposition to stress and urgency incontinence in women, with genetic variation contributing up to half of population phenotypic variability [1]. Candidate gene association studies have not however, identified any genetic variants robustly associated with either condition [2]. We conducted the first genome wide association study of stress and urgency urinary incontinence in women, aiming to identify genetic variants associated with these conditions, and to provide new insights into the molecular mechanisms and biological pathways associated with them.

METHODS

After local ethical approvals, unrelated women of European ancestry, participating in three population-representative cohorts in the UK (ALSPAC and UKTwins) and Finland (NFBC1966), self-completed postal questionnaires reporting both stress and urgency incontinence. Participants were genotyped from whole blood for up to 1.2 million Single Nucleotide Polymorphisms (SNPs), using Illumina Human Genotyping arrays. Imputation of non-genotyped SNPs and InDels was conducted with the 1000 Genomes data as a reference panel, in order to improve power to detect low frequency variants, and to enable meta-analysis between cohorts. Variants imputed with a quality metric of <0.5 (RSQR or INFO) or a minor allele frequency of <1% were excluded from analyses, giving a final total of 9.4 million directly genotyped or imputed SNPs for analysis. Primary association analyses were run separately for stress, urgency and “any” incontinence in each cohort adjusted for age, BMI, and parity, and if necessary adjusted for principal components to eliminate residual population stratification, using SNPtest or MACH2DAT. Quality control before and after meta-analysis was performed using the GWAtoolbox package in R. Meta-analyses of effect sizes from each cohort were conducted using the inverse-variance weighting method in METAL. Consequences of leading SNPs on genes and regulatory regions were tested using the Ensembl VEP tool. To further explore potential functional consequences of variants in or near genes, we measured expression of the associated gene in bladder biopsies from women with stress
or urgency incontinence, and checked for differential expression between conditions, using Affymetrix HGU133+ 2.0 microarrays.

RESULTS

8,997 women were available with both incontinence phenotypes and genotypes. The mean age of participants overall was 45 years, with median parity of 3. Sixteen SNPs at 5 independent loci exceeded the threshold for genome wide significance of p<5x10^-8 (Figure)

Figure: QQ plot for urgency incontinence demonstrating distribution of observed against expected p values.

<table>
<thead>
<tr>
<th>Locus</th>
<th>p</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>6p25.3</td>
<td>1.73x10^-8</td>
<td>Transcription Factor Binding</td>
</tr>
<tr>
<td>7p14.3</td>
<td>3.04x10^-8</td>
<td>Upstream miRNA</td>
</tr>
<tr>
<td>7q34</td>
<td>2.92x10^-8</td>
<td>Intron Variant for AGK gene</td>
</tr>
<tr>
<td>14q22.3</td>
<td>1.95x10^-8</td>
<td>Intron Variant for WDHD1 gene</td>
</tr>
<tr>
<td>20q13.13</td>
<td>8.07x10^-9</td>
<td>Transcription Factor Binding</td>
</tr>
</tbody>
</table>

Table: Top SNPs in each of five genome-wide significant loci (p<5x10^-8)

Four of the loci showed association with urgency incontinence, while one was associated with both stress and urgency incontinence. Two of the five top variants occur at transcription factor binding sites, one is an upstream variant for a novel microRNA, while two are intronic variants for the AGK and WDHD1 genes (Table). We confirmed expression of both these genes in human bladder (n=10), and identified significant differential expression in urgency incontinence for the WDHD1 gene (p=0.01). We identified 361 SNPs at a further 88 loci, with highly suggestive associations (p<5x10^-6) with one or both phenotypes. These suggestive loci include 81 genes, which we will explore further in replication cohorts.

CONCLUSIONS

Our results indicate the presence both of distinct and shared genetic susceptibility for stress and urgency incontinence, suggesting common pathophysiological mechanisms that may explain their frequent co-occurrence. Genes, transcription factor binding sites, and other regulatory elements in or near the loci identified in this study may have important roles in the aetiology of stress and urgency incontinence in women. Importantly, results reported here require external replication for confirmation. We are undertaking this replication using samples collected in other large population-based cohorts. Although the loci identified here have large effect sizes, most genome wide significant variants were rare, and even in combination would explain a small proportion of the observed heritability of these conditions, suggesting that larger meta-analyses are required in future.

REFERENCES

Genetic and environmental correlates of growth patterns leading to obesity

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² Institute of Health Sciences, University of Oulu, Oulu, Finland,
³ Unit of General Practice, Oulu University Hospital, Oulu, Finland,
⁴ Biocenter Oulu, University of Oulu, Oulu, Finland

The intrauterine period is a vulnerable period of development. Any adverse environment can permanently change the body’s organ structure and function, expressed as increased disease risk later in life. Studies show that variability in growth patterns in early life associates with obesity, and other cardiovascular diseases in adulthood, but the genetic and environmental determinants of these processes are largely unknown. The main objectives of this study were to identify genetic and environmental prenatal and postnatal factors associated with early growth in infancy and childhood and later metabolic outcomes in adulthood from the Northern Finland Birth Cohorts (NFBCs).

Several maternal and paternal factors, such as height, smoking, parity and pre-eclampsia, had direct association with faster postnatal height growth, some of which had their association mediated by size-at-birth variables. It was observed that obesogenic environment in-utero and during child’s growth exerts a ‘programming’ effect on the glucose-insulin axis as well as cardio-vascular risk factors in adolescence. Moreover, the study shows that Leukocyte Telomere Length (LTL) at 31 years, a marker for aging, inversely associated with multiple measures of adiposity in both men and women, and that BMI increase in women from childhood to adulthood is associated with shorter telomeres at age 31. Two new variants in/near SBNO1 and HMGA2 associated with infant head circumference, which may indicate influence of brain growth and neurodevelopment via early life. Variants in/near LEPR-LEPROT, FTO, TFAP2B and GNPDA2 showed an age-dependent association with adiposity in early childhood, with three loci (FTO, TFAP2B and GNPDA2) had their effect on adult adiposity mediated by early growth phenotypes.

The study emphasises clinical importance of early growth markers as it may inform public health policy aimed to improve the pre-pregnancy environment and also monitor infant’s growth during the first few years.
Dispositional optimism in NFBC-1966, relations and antecedents

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INTRODUCTION

Dispositional optimism can be regarded as the generalized tendency to expect positive outcomes or the belief that “good rather than bad things will happen in a person’s life” (1). As such, it creates a sense of security, and has been found to associate strongly with both physical and psychological health and well-being. Also, as individuals’ expectancies of eventual success are sufficiently favourable, they are likely to remain engaged in efforts to reach desired goals despite adversities that may arise (2). Therefore, not surprisingly, dispositional optimism has been found to associate with different types of health behavior. By the 31-year follow up in the NFBC-1966, there had been, however, only little research among younger normal populations, while the positive effects on health and well-being among the elderly was quite well demonstrated. Additionally, longitudinal research on dispositional optimism was then almost non-existent. As theoretical starting points, previous research on other related positive psychological constructs, previous research on depression, and life span research were used.

METHODS

At 31-year follow up, the Life Orientation Test (LOT-R) developed by Scheier and Carver (1) was introduced to NFBC-1966, and it was also used in the 46-year follow up. The test assesses individual differences in generalized future outcome expectations, associating positive expectations with optimism and negative ones with pessimism. The LOT-R consists of six items, three of which are keyed in a positive direction, and the other three in a negative direction (see Table 1 for details).

<table>
<thead>
<tr>
<th>Items</th>
<th>α = 0.78</th>
</tr>
</thead>
<tbody>
<tr>
<td>I rarely count on good things happening to me.</td>
<td></td>
</tr>
<tr>
<td>I hardly ever expect things to go my way.</td>
<td></td>
</tr>
<tr>
<td>If something can go wrong for me, it will.</td>
<td></td>
</tr>
<tr>
<td>Overall, I expect more good things to happen to me than bad.</td>
<td></td>
</tr>
<tr>
<td>I am always optimistic about my future.</td>
<td></td>
</tr>
<tr>
<td>In uncertain times I usually expect the best.</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Items in LOT-R.

Relations to health behavior, and social and psychological correlates of dispositional optimism were studied using the 31-year questionnaire data. The antecedents of dispositional optimism were studied using both earlier (0/1 year and 14 year) questionnaire data and register data.

RESULTS

Lack of optimism, also among young adults, was found to be associated with unhealthy dietary habits, smoking and alcohol use (3), and with facial pain (4). Positive effects of dispositional optimism were found on young adults’ subjective health, life satisfaction and general health behavior (5), as well as on dental health behavior through the mediating role of active coping (6).

At 31 years, the optimists in NFB-1966 were more often married or cohabiting than the pessimists, had higher annual incomes and
had a higher basic and vocational education (3, 7). Those who had migrated by 31 years of age from rural to urban areas were more likely to use active coping strategies and to have an optimistic attitude towards the future than those who had stayed in rural areas (8).

School achievement in adolescence, the families’ SES in adolescence and the cohort members’ work history were strong predictors of the level of dispositional optimism in early adulthood. Having been born wanted in 1966 predicted the cohort members’ level of optimism 31 years later, while the mother’s depressiveness during pregnancy predicted a low level of optimism only among men 31 years later. (7)

**CONCLUSIONS**

The results from the 31-year follow-up have shown that also among young adults, dispositional optimism associates strongly with well-being and health behavior. The results on correlates and antecedents of dispositional optimism emphasize the social foundation of dispositional optimism. A critical social element in the development of optimism seems to be success in the developmental task typical for a certain age, such as educational achievement in adolescence and work history in early adulthood. In the NFBC-1966 study, it is possible in the future to further examine the developmental paths of dispositional optimism to later adulthood, especially the role of career pathways and work conditions during the work career. Also, the role of dispositional optimism/pessimism at the beginning of a work career in possibly predicting later career pathways needs to be examined.

**REFERENCES**

Comparison of risk factors of psychoses between the Northern Finland Birth Cohorts 1966 and 1986

Filatova Svetlana¹, Keskinen Emmi², Mäki Pirjo³, Moilanen Kristiina⁴, Mustonen Antti⁵, Lassila Meri⁶, Nordström Tanja⁷, Marttila Riikka⁸, Kyllonen Merja⁹, Veijola Juha¹⁰, Murray Graham¹¹, Koivumaa-Honkanen Heli¹², Isohanni Matti¹³, Jääskeläinen Erika¹⁴, Miettunen Jouko¹⁵

INTRODUCTION

Schizophrenia and other psychotic disorders are a major public health problem and leading unsolved disease afflicting about 3-4% of the population. We have previously studied psychosis risk factors especially in the NFBC 1966 (1). The aim of this project is to expand the research tradition utilizing the prospective cohort design with two large cohorts and novel methods.

METHODS

The study sample consisted of two general population based birth cohorts: the Northern Finland Birth Cohort 1966 (NFBC 1966,
12058 live born children) and 1986 (NFBC 1986, N= 9432). The individuals with psychotic disorders have been detected from different national registers (hospitalizations, outpatient visits, sick leaves, disability pensions, and reimbursable medicines). The incidence of psychoses and risk factors were compared until age of 27 years in both genders.

RESULTS

The lifetime cumulative incidence of psychoses was 1.2% (140/11689) in the NFBC 1966 and 1.9% (177/9222) in the NFBC 1986. Of the psychotic cases, the NFBC 1966 cohort included more schizophrenia spectrum cases than NFBC 1986 (0.06% vs. 0.03%), whereas NFBC 1986 had relative more affective psychoses (0.12% vs. 0.25%) (Filatova et al. Manuscript). The Figure 1 compares onset age for psychosis between cohorts and genders. In the younger birth cohort more female cases were detected, especially before age of 20 years.

Figure 1. Onset age for psychosis by gender and the birth cohort.

Parental psychosis related to psychosis risk in both the cohorts; in the NFBC 1966 hazard ratio (HR) was 2.36 (95% confidence interval, 1.47-3.79) and in the NFBC 1986 HR was 2.99 (1.91-4.67). Unwanted pregnancy was much more common in the NFBC 1966 than in the NFBC 1986 (11.5% vs. 1.0%). Unwanted pregnancy was a trend-level risk factor in the NFBC 1966 (HR: 1.90, 95% confidence interval, 0.98-3.68) but did not associate with psychosis in the NFBC 1986. Cannabis use was a risk factor in the NFBC 1986 (HR: 2.73, 95% confidence interval, 1.61-4.63) (Mustonen et al. Manuscript), in the adolescence of the NFBC 1966 members it was not used in the Northern Finland.

CONCLUSIONS

In NFBC 1986 females have an onset of psychosis at younger age compared to females in NFBC 1966. When comparing two cohorts there is the shift from schizophrenia to affective psychoses.

We were able to detect differences in number of psychoses between two comparable cohorts, which differed 20 years in time.

In future, we will compare the cohorts also regarding school success and motor development as risk factors for psychoses.

REFERENCES

INTRODUCTION

Maternal body mass index [BMI], birth weight and preschool BMI may help identify children at high risk of overweight as they are 1) similarly linked to adolescent overweight at different stages of the obesity epidemic, 2) linked to adult overweight and metabolic alterations, and 3) easily obtainable in health examinations in young children.

The aim of this study is to develop models to predict adolescent overweight, adult obesity and adult metabolic syndrome at the ages of 1-8 years. We especially aimed at exploring prediction models using routinely available data from the preceding and concurrent examination at the age of 5 years.

METHODS

We developed prediction models at various ages in the Northern Finland Birth Cohort born in 1966 [NFBC1966] (N=4111). Internal validation was tested using a bootstrap design and external validation was tested for the model predicting adolescent overweight using the Northern Finland Birth Cohort born in 1986 [NFBC1986] (N=5414). The area under the ROC curve [AUC] is equal to the probability (here represented as percentages) that the model will rank a randomly chosen case higher in risk than a randomly chosen non-case. AUC above 50% represents a classification better than random and 100% represents the perfect classification.

RESULTS

The figure shows the AUC development when prediction models with the outcome of adolescent overweight are developed with increasing age from birth to the age of 8 years in the NFBC1966. A prediction model developed at the age of 5 years in the NFBC1966, applied to the NFBC1986, and aimed at labeling 10% as “at
risk”, identified one third of all the children actually becoming overweight in adolescence.

CONCLUSIONS

The present prediction model confidently identified a subgroup of children at very high risk and identified another large proportion of individuals at very low risk.
Stability of the associations between early life risk indicators and adolescent overweight over the evolving obesity epidemic

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INTRODUCTION

Pre- and perinatal factors and preschool body size may help identify children developing overweight, but these factors might have changed during the development of the obesity epidemic. We aimed to assess the associations between early life risk indicators and overweight at the age of 9 and 15 years at different stages of the obesity epidemic.

METHODS

We used two population-based Northern Finland Birth Cohorts including 4111 children born in 1966 (NFBC1966) and 5414 children born in 1985-1986 (NFBC1986). In both cohorts, we used the same a priori defined prenatal factors, maternal body mass index (BMI), birth weight, and growth curves to extract infant weight (age 5 months and 1 year), and preschool BMI (age 2-5 years). We used internal references in early childhood to define percentiles of body size (<50, 50-75, 75-90 and >90) and generalized linear models to study the association with overweight, according to the International Obesity Taskforce (IOTF) definitions, at the ages of 9 and 15 years.

RESULTS

The prevalence of overweight at the age of 15 was 9% for children born in 1966 and 16% for children born in 1986. However, medians of infant weight and preschool BMI changed little between the cohorts, and we found similar associations between maternal BMI, infant weight, preschool BMI, and later overweight in the two cohorts. At 5 years, children above the 90th percentile had approximately a 12 times higher risk of being overweight at the age of 15 years.
compared to children below the 50th percentile in both cohorts (Table 1).

**CONCLUSIONS**

The associations between early body size and adolescent overweight showed remarkable stability, despite the increase in prevalence of overweight over the 20 years between the cohorts. Using consequently defined internal percentiles may be a valuable tool in clinical practice.

**REFERENCE**


<table>
<thead>
<tr>
<th>NFBC66 (N=1911)</th>
<th>N</th>
<th>n(%)</th>
<th>RR(95%CI)</th>
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<tr>
<td>BMI at 5 years (kg/m$^2$)</td>
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<tr>
<td>&lt; 50 percentile</td>
<td>952</td>
<td>24(3)</td>
<td>1</td>
</tr>
<tr>
<td>$\geq$ 50 - &lt;75</td>
<td>475</td>
<td>31(7)</td>
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<tr>
<td>$\geq$ 75 - &lt;90</td>
<td>290</td>
<td>45(16)</td>
<td>6.2(3.9-10.1)</td>
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<tr>
<td>$\geq$ 90</td>
<td>194</td>
<td>67(35)</td>
<td>13.5(8.7-21.0)</td>
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<table>
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<tr>
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<th>N</th>
<th>n(%)</th>
<th>RR(95%CI)</th>
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<td>BMI at 5 years (kg/m$^2$)</td>
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<td></td>
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<tr>
<td>&lt; 50 percentile</td>
<td>1876</td>
<td>89(5)</td>
<td>1</td>
</tr>
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<td>$\geq$ 50 - &lt;75</td>
<td>920</td>
<td>129(14)</td>
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<td>$\geq$ 75 - &lt;90</td>
<td>549</td>
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<td>$\geq$ 90</td>
<td>364</td>
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<table>
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<th>N</th>
<th>n(%)</th>
<th>RR(95%CI)</th>
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<tr>
<td>$\geq$ 90</td>
<td>558</td>
<td>261(47)</td>
<td>11.7(9.6-14.3)</td>
</tr>
</tbody>
</table>

*Table 1*: Relative risk of overweight at the age of 15 years according to the IOTF associated with BMI at the age of 5 years in the NFBC1966 and the NFBC1986. No statistically significant differences were found between cohorts or genders.
Preschool weight and body mass index in relation to central obesity and metabolic syndrome in adulthood

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INTRODUCTION

If preschool measures of body size routinely collected at preventive health examinations are associated with adult central obesity and metabolic syndrome, a focused use of these data for the identification of high risk children is possible. The aim of this study was to test the associations between preschool weight and body mass index (BMI) and adult BMI, central obesity and metabolic alterations.

METHODS

The Northern Finland Birth Cohort 1966 (NFBC1966) (N=4111) is a population-based cohort. Preschool weight (age 5 months and 1 year) and BMI (age 2-5 years) were extracted from estimated growth curves and studied in relation to metabolic syndrome as well as BMI, waist circumference, lipoproteins, blood pressure, and fasting glucose at the age of 31 years. Linear regression models and generalized linear regression models with log link were used.

RESULTS

Throughout preschool ages, weight and BMI were significantly linearly associated with adult BMI (figure 1) and waist circumference. Preschool BMI was inversely associated with high-density lipoprotein levels from the age of 3 years. Compared with children in the lower half of the BMI range, the group of children with the 5% highest BMI at the age of 5 years had a relative risk of adult obesity of 6.2 (95% CI:4.2-9.3), of adult central obesity of 2.4 (95% CI:2.0-2.9), and of early onset adult metabolic syndrome of 2.5 (95% CI:1.7-3.8).

CONCLUSIONS

High preschool BMI is consistently associated with adult obesity, central obesity and early onset metabolic syndrome.
Routinely collected measures of body size in preschool ages can help to identify children in need of focused prevention due to their increased risk of adverse metabolic alterations in adulthood.

**REFERENCE**


**Figure 1:** Relationship between preschool body size and body mass index (BMI) at the age of 31 years. Differences in the dependent variable in adulthood per kg or BMI unit in childhood are shown as percentages (x axis). Unadjusted associations (solid dots) and associations adjusted for birth weight, gestational week, maternal smoking during pregnancy, maternal age at birth, maternal pre-pregnancy BMI, maternal education and parity (circles) are presented with their 95% confidence interval.

* represents a statistically significant difference between genders.
Brain structural changes in women and men during midlife

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INTRODUCTION

Brain development during childhood and adolescence differs between boys and girls. Structural changes continue during adulthood and old age, particularly in terms of brain volume reduction that accelerates beyond age 35 years. We investigated whether brain structural change in mid-adult life differs between men and women and where in the brain these differences occur.

METHODS

43 men and 28 women were randomly selected from the Northern Finland 1966 Birth Cohort, and underwent MRI brain scans at age 33-35 (SD = 0.67) and then again at age 42-44 (SD = 0.41). We examined gender differences in total percentage brain volume change (PBVC) and regional brain change with FSL SIENA software.

RESULTS

Women showed significant PBVC reduction compared with men between the ages of 33-35 and 42-44 years (Mean = -3.48% in men, Mean = -4.97% in women, F (1, 68) = 24.84, p < 0.001). In regional analyses, women exhibited greater brain reduction than men in widespread areas of frontal cortex, parietal cortex, superior temporal cortex, inferior occipital cortex, cerebellum and brain stem. After controlling for total percent brain volume change, men show greater relative regional brain reduction than women in bilateral precentral gyri, bilateral paracingulate gyri, and bilateral supplementary motor cortices.

CONCLUSIONS

There are sex differences in brain changes in mid-life. Women have more brain reduction on the outer brain surface than men, whereas men exhibit more brain reduction on the mid-line surface than women after co-varying for total brain volume loss. These changes could contribute to sex differences in midlife behaviour and risk for mental illness.
Speech and language difficulties and associated psychiatric problems: a 16-year follow-up in the northern Finland 1986 birth cohort

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INTRODUCTION

Research on childhood speech and language difficulties (SLDs) and psychosocial problems is quite expansive¹. Associations between childhood SLDs and psychiatric disorders, especially Attention Deficit Hyperactivity Disorder (ADHD)² and pragmatic language impairment, behavioural problems and hyperactivity³ are well established. The association between SLDs and behavioural problems seems to be strong also the other way round. For example, children referred to child psychiatric services manifesting behavioural problems also had language impairment that was not previously diagnosed⁴. Moreover, in adolescence, Bryan and colleagues found elevated levels of SLDs when measured with standardized tests among juvenile offenders. In the present study we hypothesized that childhood SLDs may have consequences on later mental health. We investigated whether the SLDs at 8 years predict behavioural and emotional problems, and whether SLDs affect psychosocial wellbeing in 16-year-old adolescents from general population.

METHODS

The original study population consists of 9432 live born children, whose expected date of birth fell between July 1st 1985 and June 30th 1986. All the mothers living in the two northernmost provinces of Finland, Oulu and Lapland, were recruited (99.6%). At the time of the first follow-up, when the children were seven and eight years old, 99% (n=9357) of them were alive⁵. The second follow-up study started in 2001, when the adolescents were 15-16 years old⁵. At this phase 99% (n=9340) of the adolescents were alive and the residence was known for 9215 adolescents.

In the spring near the end of the children’s first school year, the parents assessed children’s speech and language difficulties, both speech production and reception (response rate n=8370, 90%) and the teachers assessed children’s behaviour and emotional problems using Rutter Scale (response rate n=8525, 92%).

The second follow-up included postal questionnaires to parents and adolescents. In their questionnaire parents assessed adolescents’ behaviour and adolescents assessed their wellbeing. Eighty percent (n=7344) of the adolescents and 76% (n=6985) of the parents returned the questionnaire. In addition with the questionnaire both SWAN scale and Youth Self Report (YSR) were used.

RESULTS

Those who had SLDs at eight years also demonstrated concurrent behavioural (26% vs. 20%, p<.001) and emotional (32% vs. 20%, p<.001) problems. When studying boys and girls separately, statistically significant
associations were found between SLDs and emotional problems. No significant differences were found between components of SLDs and behavioural and emotional problems.

Those with SLDs and behavioural problems at eight years had more adolescent behavioural problems (24% vs. 21%, p=.031) than those without SLDs but having behavioural problems at eight years. There was no significant difference in adolescent behavioural problems between those with and without SLDs and no childhood behavioural problems.

Those with SLDs and emotional problems at eight years had more adolescent emotional problems (23% vs. 15%, p=.001) than those without SLDs but having emotional problems at eight years (Figure 1).

CONCLUSIONS

To summarize, we could argue that problems in speech and language are a risk for later psychiatric problems such as behavioral, emotional and ADHD symptoms in adolescence. At school age and at early adulthood there is no possibility to get any services provided by speech and language therapists even though it has been noted that children even at the 8th grade have problems in their speech production.

REFERENCES


Development of schizophrenia from a lifespan perspective within the Northern Finland 1966 Birth Cohort

Isohanni Matti

INTRODUCTION

Schizophrenia and other psychotic disorders are a major public health problem and leading unsolved disease affecting about 3-4% of the population. Schizophrenia is generally but not always a lifelong condition. Despite excess mortality, most survive into old age. Subtle motor, emotional, cognitive and behavioural abnormalities are often present in apparent healthy children and adolescents who later develop schizophrenia. This suggests that some aspects of causation are established long before psychosis is manifest. We have previously studied psychosis risk factors especially in the NFBC 1966 (1). The aim of this project is to expand this research tradition utilizing the prospective cohort design with life span view.

METHODS

The individuals with psychotic disorders have been detected from different registers (hospitalizations, outpatient visits, sick leaves, disability pensions, and reimbursable medicines) and multiple follow-ups. Structural and functional MRI, cognitive, and clinical analyses were performed at ages 34 and 43.

RESULTS

Multiple risk factors related to later schizophrenia were detected: unwanted pregnancy, obstetric and delivery complications, slow development, scholastic problems. Brain matter deficits, cognitive decline, excess somatic comorbidity and mortality were found during the midlife between ages 34 and 43 years. High dose years of antipsychotic medication correlated with increased brain volume loss (2). We also observed general disease progression: relatively poor prognosis and many relapses, excess mortality and somatic comorbidity, and limited occupational capacity.

CONCLUSIONS

Schizophrenia progresses in midlife. High doses of antipsychotics were related to accelerated brain volume loss. Brain volume, verbal learning and memory reduction occurs in schizophrenia long after the onset of illness, and antipsychotic medications may contribute to these reductions. A deteriorating general course of schizophrenia for some individuals during midlife (3) may reflect these brain abnormalities and reduce adult well-being and creativity typical to this epoch. and, Very few prospective longitudinal studies have analysed trajectories from early-mid adulthood into old age. In this review, we present current knowledge of the progression of schizophrenia into later life and its related characteristics. Our main conclusion is that, while the course in later life is variable and the condition frequently stable, many people remain symptomatic and impaired, and mortality and somatic comorbidity increase.

The diagnosis of schizophrenia is often delayed or conservative. Prevention of unwanted pregnancies may influence the incidence of schizophrenia. Brain volume alterations (mainly loss) and cognitive deviances exist in schizophrenia and may
progress in midlife. Clinical and occupational outcomes in schizophrenia are not as good as they could be: recovery is uncommon and educational and occupational outcomes unsatisfactory. Metabolic problems and altered lipid profiles begin in schizophrenia patients during their 30s but adverse clinical manifestations appear later; there exists a window for intervention to reduce cardiovascular related mortality. Excess mortality, primarily due to suicide, is a clinical reality in schizophrenia. Long duration of untreated psychosis (DUP) predicts poorer short-term but not long-term outcome; this result both supports and challenges early detection of psychoses.

Improvements and optimization of care in schizophrenia are needed. In addition to RCTs, observational and naturalistic studies like NFBC 1966 may give data how optimal care should be realized.

REFERENCES


Central executive network in young people with familial risk for psychosis – the Oulu brain and mind study

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INTRODUCTION

The function of large-scale neurocognitive networks are thought to provide important insights into psychiatric and neurological disorders.¹ ² One of these networks is called the central executive network (CEN) that is localized in fronto-parietal regions, including dorsolateral prefrontal cortex and lateral posterior parietal cortex.³

The CEN contributes to many high-level neurocognitive functions such as working memory, planning, problem solving and decision making.² ⁴ The CEN plays important role in strategy selection, verbal fluency, dual-task performance, switching of retrieval strategy, inhibiting irrelevant effects, holding and manipulating information in long-term memory and updating processes.⁵

The CEN has strong connectivity to other two major cognitive control networks: the salience network and the default mode network.⁶ In cooperation with the salience network, the CEN forms a neural switch that swaps brain states from the task-negative default mode network to task-positive networks and vice versa.⁶

Abnormal function in the CEN has been related to major psychiatric and neurological disorders, including psychosis and schizophrenia.⁷ A few studies have suggested functional alterations in the CEN area are evident in subjects with familial risk for psychosis (FR).⁸

In the present Oulu Brain and Mind study we applied spatial domain independent component analysis (ICA) to R-fMRI data in order to analyze 72 young FR participants and 72 control subjects without parental psychosis. The two groups were well-matched as they were both drawn from the Northern Finland Birth Cohort 1986 (NFBC 1986). To the best of our knowledge this was the first general population based R-fMRI study using birth cohort data to probe the function of the CEN in subjects with FR for psychosis.

RESULTS

FR participants demonstrated statistically significantly lower activity compared to control subjects in the right inferior frontal gyrus, a key node of CEN corresponding to Brodmann areas 44 and 45 (Fig. 1).
Figure 1. Yellow and orange colors representing the central executive network based on the independent component analysis using model order 30 with respective t-score thresholding on right. Participant with familial risk for psychosis showed (in green color) statistically lower connectivity in 254 mm³ area in the right inferior frontal gyrus.

CONCLUSIONS

The activity of the CEN differed in the right inferior frontal gyrus between FR and control groups. This suggests that abnormality of right inferior frontal gyrus is central part of vulnerability for psychosis.

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Outcome of schizophrenia in the Northern Finland Birth Cohort 1966

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INTRODUCTION

Schizophrenia is one of the most severe mental illnesses. It causes marked impairments in social, occupational, and cognitive functioning, increased mortality and somatic comorbidity, as well as stigma. Recovery is possible, though not very common (13.5%), and disappointingly it has not increased during last decades. Several factors has been associated to poorer outcomes in schizophrenia, for example long duration of untreated psychosis (DUP) and family history of psychosis.

The aim of this project is to analyse the longitudinal course of illness and several outcomes and their predictors in schizophrenia in the Northern Finland Birth Cohort 1966. In the future, this project will result in at least four doctoral thesis and several original research articles.

METHODS

The project will utilize the Northern Finland Birth Cohort 1966 (NFBC 1966). We have collected detailed information about diagnoses and longitudinal outcomes and outcome predictors for over 100 persons with schizophrenia. Of these, approximately 40 individuals with schizophrenia and 77 controls have participated twice in psychiatric examinations, including cognitive tests, interviews and brain MRI (magnetic resonance imaging).

RESULTS

Outcomes. The outcome in schizophrenia was heterogeneous in the NFBC 1966. Recovery was not common (3.4%), whereas re-hospitalization was (80%). 7% of schizophrenia cases had committed suicide. Most (85%) use antipsychotics, and most often atypical antipsychotics.

Predictors of outcomes. We have found clinically relevant predictors of poor outcomes:

- early age of illness onset
- longer, but also shorter DUP
- presence of negative and depressive symptoms at first episode
- suicidal ideation at first episode
- short first hospitalization
- please see references

Additionally, later motor development at age 1 year did not relate to poorer course of illness; but instead subtly with better prognosis. A difference in brain morphology between subjects with good and poor outcomes was found. This difference may reflect separable aetiologies and developmental trajectories in schizophrenia.

Longitudinal course of cognition. In 9-year
follow-up from 34-years to 43-years, both persons with schizophrenia and non-psychotics controls deteriorated in verbal learning and memory. The decline mostly was not significantly larger in cases. It seems that during midlife verbal learning and memory in schizophrenia mostly declines in a normative fashion with aging, and this indicates that schizophrenia may not be degenerative illness.11

CONCLUSIONS

Our results indicate heterogeneous and still relatively unsatisfactory prognosis of schizophrenia. However, there does not seem to be a major cognitive decline from 34-years to 43-years of age.

In clinical practice, the prognosis of schizophrenia may be enhanced by early detection and intervention in first episode of psychosis, and paying special attention to those patients having markers of possibly poorer prognosis, for example those having long duration of untreated psychosis, early age of illness onset, and more severe illness around the first episode.

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Genetic determinants of early growth and development – new dawn of longitudinal studies

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Many early life developmental phenotypes such as birth weight, birth length, gestational age, and postnatal growth are known to associate with later life disease or disorder risk. The mechanisms underlying these associations are poorly understood and may represent intrauterine programming or two phenotypes of one or more genotypes. We have conducted candidate gene and genome-wide association studies (GWAS) as well as other large scale analyses using multiple datasets since early 2000 to identify genetic and environmental determinants of early growth and development.

We have used data from several internationally well-known birth cohorts including Northern Finland Birth Cohorts and Helsinki Birth Cohort from Finland, Avon Longitudinal Study on Parents and Children and British 1958 Birth Cohort from the UK, and samples from the Netherlands, Australia, and the USA among others.

In the latest GWAS study of birth weight on over 69,000 individuals of European descent from 43 studies, we have extended the number of genome-wide significant loci from two (1) to seven (2). Five of the loci are known to be associated with other phenotypes: ADCY5 and CDKAL1 with type 2 diabetes; ADRB1 with adult blood pressure; HMGA2 and LCORL with adult height and LCORL also with peak height velocity in infancy (3). Our findings highlight that there is a genetic link between fetal growth and postnatal growth and metabolism, in addition to potential nutritional programming. We were also able to show that early life stress may modify the association between genetic variant and size at birth (4).

In addition, we have performed candidate gene studies for birth weight (5) and GWAS for other early growth and developmental phenotypes such as body mass growth patterns in childhood and tooth development. For tooth development we identified variants in several genes with link to other organ development or disease (6). This kind of studies may to some extent help to resolve the complex chains of causality underlying the associations between early events and later health.

Acknowledgements: We sincerely thank for EGG consortium members for their outstanding work.
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Stress-related eating, obesity and associated behavioral traits in adolescents: a prospective population-based cohort study

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INTRODUCTION

Stress-related eating is associated with unhealthy eating and drinking habits and an increased risk of obesity among adults¹, but less is known about factors related to stress-driven eating behaviour among children and adolescents. We studied the prevalence of stress-related eating and its association with overweight, obesity, abdominal obesity, dietary and other health behaviours at the age of 16. Furthermore, we examined whether stress-related eating is predicted by early-life factors including birth size and maternal gestational health.

The study was supported by the SalWe Research Programme for Mind and Body (Tekes – the Finnish Funding Agency for Technology and Innovation grant 1104/10).

METHODS

The study population comprised 3598 girls and 3347 boys from the Northern Finland Birth Cohort 1986. Followed up since their antenatal period, adolescents underwent a clinical examination, and their stress-related eating behaviour, dietary habits and other health behaviours were assessed using a postal questionnaire. We examined associations using crosstabulations followed by latent class analysis and logistic regression to profile the adolescents and explain the risk of obesity with behavioural traits.

RESULTS

Stress-related eating behaviour was more common among girls (43%) than among boys (15%). Compared with non-stress-driven eaters, stress-driven eaters had a higher prevalence of overweight, obesity and abdominal obesity. We found no significant associations between stress-eating and early-life factors. Among girls, tobacco use, shorter sleep, infrequent family meals and frequent consumption of chocolate, sweets, hamburgers and pizza were greater among stress-driven eaters. For both genders, the proportions of those bingeing and using heavy exercise and strict diet for weight control were higher among stress-eaters. Besides a ‘healthy lifestyle’ cluster, latent class analysis revealed two other patterns (‘adverse habits’, unbalanced weight control’) that significantly explained the risk of overweight among boys and girls.
CONCLUSIONS

Stress-related eating is highly prevalent among 16-year-old girls and is associated with obesity as well as adverse dietary and other health behaviours among both genders, but intrauterine conditions are seemingly uninvolved. In terms of obesity prevention and future health, adolescents who use eating as a passive way of coping could benefit from learning healthier strategies for stress and weight management.

REFERENCES

Psychosocial factors at work and obesity among young Finnish adults: a cohort study

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INTRODUCTION

Obesity and occupational stress are important public health concerns due to their large yet preventable disease burdens¹. We examined the associations between occupational psychosocial factors and obesity among 31-year-old men and women, and determined whether these associations are modified by childhood body mass index (BMI), physical strenuousness of work and adverse health behaviours, i.e. stress-related eating, physical inactivity, smoking, and high alcohol consumption.

The study was supported by the SalWe Research Programme for Mind and Body (Tekes – the Finnish Funding Agency for Technology and Innovation grant 1104/10).

METHODS

The study sample consisted of 2083 men and 1770 women from the Northern Finland Birth Cohort 1966. At the 31-year follow-up, participants underwent a clinical examination and their health behaviours were assessed using a postal questionnaire. Obesity was defined as BMI ≥30.0 kg/m². Psychosocial exposures were defined in terms of demands, control and social support at work². Associations were examined using logistic regression.

RESULTS

Among men, high job demands (OR 2.0, 95% CI 1.2-3.3) and low worksite social support (OR 1.8, 95% CI 1.1-2.8) was independently associated with obesity. Among women, no associations between occupational psychosocial factors and obesity were detected. BMI at age 14 was an important predictor of obesity for both genders. Regarding health behaviours, among men, high alcohol consumption and leisure-time physical inactivity, and among women, stress-related eating and drinking and infrequent leisure-time exercise appeared to promote obesity.

CONCLUSIONS

High demands and low social support at work were associated with increased odds of obesity for men, whereas for women, behavioural factors outweighed working conditions as determinants of obesity. These results suggest that in workplace obesity prevention programmes, it is beneficial to improve the psychosocial work environment and promote healthy behaviours simultaneously.
REFERENCES


Association between occupational psychosocial factors and waist circumference is modified by diet among men: a population-based study

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INTRODUCTION

Occupational psychosocial stress has been identified as a risk factor for obesity\textsuperscript{1} whereas dietary habits play a key role in weight control\textsuperscript{2}. We examined whether dietary habits modify the association between occupational psychosocial factors and waist circumference in young Finnish adults.

The study was supported by the SalWe Research Programme for Mind and Body (Tekes – the Finnish Funding Agency for Technology and Innovation grant 1104/10).

METHODS

We used data from 31-year-old men (n=2222) and women (n=2053) belonging to the Northern Finland Birth Cohort 1966. Waist circumference was measured and data on occupational psychosocial factors (demands, control and social support) and other characteristics were obtained through questionnaires. Healthy and unhealthy diet indices were constructed according to the current dietary guidelines. Associations were examined using analysis of variance adjusted for body mass index at age 14, basic education level, leisure-time physical activity, alcohol consumption, smoking, stress-related eating behaviour and parity.

RESULTS

Among men, high job demands and high job control were associated with greater waist circumferences and there were interactions between unhealthy diet and job demands (p=0.043) and job control (p=0.036) in relation to waist circumference. The waist of men with high demands or high control and low consumption of unhealthy foods (red or processed meat, hamburgers and pizzas, fried potatoes, sugar-sweetened soft drink, white bread) was smaller than that of men with high demands or high control and high consumption of such foods. No associations were found among women.

CONCLUSIONS

A diet based on the current dietary guidelines seems to cancel out the adverse effects of occupational psychosocial stress on waist circumference among young men. Longitudinal studies are needed to assess the risk for obesity-related diseases arising from psychosocial work environments and dietary habits.
REFERENCES


Antipsychotic medication and its’ association on
cognition, brain and course of illness in schizophrenia
in the Northern Finland Birth Cohort 1966

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INTRODUCTION

Brain abnormalities and cognitive deficits are fundamental features of schizophrenia. There is growing evidence that some of the neuroanatomical alterations and brain volume loss in schizophrenia may be associated with antipsychotic treatment (1). High doses of antipsychotics may also have a role in cognitive impairments.

The aim of this project is to analyze the association between use and dose of antipsychotic medication and brain volumes, cognition and longitudinal course of illness in schizophrenia in the Northern Finland Birth Cohort 1966.

METHODS

The project will utilize the Northern Finland Birth Cohort 1966. We have collected detailed information about diagnoses, longitudinal outcomes and lifetime use of antipsychotic medications for over 55 persons with schizophrenia. Of these, approximately 40 individuals with
schizophrenia participated twice to psychiatric examinations, including cognitive tests, interviews and brain MRI.

RESULTS

In the NFBC 1966 34% of schizophrenia cases were without antipsychotics after in average ten years after onset of illness (2). In schizophrenia, high dose of antipsychotics may contribute to decrease of total brain volume (Veijola et al. in review, Figure 1).

Figure 1. Association between higher cumulative scan-interval dose of antipsychotic medication and more decrease of total brain volume in schizophrenia.

Additionally, high cumulative life-time use of antipsychotics associated to decrease of cognitive functioning in 9-year follow-up persisting after adjustment with severity of illness (Husa et al. Manuscript).

Early antipsychotic-free period associated in trend-level (p=0.078) positively with likelihood of remission at the age of 43 years (Moilanen et al. Manuscript).

Additionally, among those without psychosis diagnosis, high doses of antipsychotics associated to suicidal ideation (3).

CONCLUSIONS

Based on our data, the use of high doses of antipsychotics may be associated with some decline in cognition and brain volumes in schizophrenia. These results do not support the view that antipsychotics in general prevent cognitive decline or promote cognitive recovery in schizophrenia. In the future, more longitudinal research on the effects of very long-term antipsychotic use on cognition and brain volumes, with larger sample sizes is needed.

REFERENCES

Genetic and life course determinants of cardiovascular risk factors: structural equation modelling of complex relations

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Cardiovascular disease is currently the leading cause of mortality worldwide. Several factors contribute to its development, including increased body mass index, high blood pressure and smoking. Many genetic and behavioural determinants of these risk factors have been identified, but the interplay between them along the life course is still poorly understood. Life course epidemiology and statistical methods developed for life course studies are required to enhance understanding of the aetiologies of these risk factors for more effective prevention and treatment of cardiovascular disease.

In this project, structural equation modelling was applied 1) to estimate the effect of variation in the fat mass and obesity – associated gene, \(FTO\), on body mass index over the life course; 2) to identify sensitive periods of growth in influencing adult blood pressure; and 3) to identify developmental changes in the effects of two confirmed genetic loci, \(TTC12-ANKK1-DRD2\) and \(CHRNA5-CHRNA3-CHRNB4\), affecting smoking behaviour. Additionally, pleiotropic effects of the variation in \(CHRNA5-CHRNA3-CHRNB4\) on smoking, body mass index and blood pressure were studied. The study population was based on the Northern Finland Birth Cohort 1966 with data available from early gestation until the age of 31 years (\(N \sim 6000\)).

The first study indicated that the effect of the \(FTO\) variant on body mass index changes over time, with strengthening of the effect by age. The results from the second study demonstrated the important role of both prenatal and postnatal growth in determining adult blood pressure. In the third study, \(TTC12-ANKK1-DRD2\) was shown to influence the initiation of smoking, while \(CHRNA5-CHRNA3-CHRNB4\) was associated with smoking persistence. Finally, some evidence was found for pleiotropic effects of the \(CHRNA5-CHRNA3-CHRNB4\) gene cluster on the three traits of interest. Results from all the studies emphasised the importance of environmental and behavioural factors in determining adult metabolic profile, in addition to genetic predisposition.

This study demonstrated the usefulness of life course studies in detecting age-varying genetic effects, and provided new insights into the already identified factors associated with cardiovascular disease risk. The findings also emphasise early interventions and lifestyle guidance for long-term benefits in health.

REFERENCES


**Figure 1.** SEM model for smoking behaviour. Path coefficients are standardised probit regression estimates, and thicknesses of path lines are proportional to the estimates. Paths with P-value >0.05 are shown with dashed lines. Maternal smoking and smoking at 14 years: smokers are compared with non-smokers; smoking at 31 years: heavy smokers are compared with light/non-smokers.
Musculoskeletal research in Northern Finland Birth Cohorts

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Musculoskeletal (MS) research in Northern Finland Birth Cohorts (NFBC) started in 1998 with a register-based study on the incidence of hospitalizations due to low back disorders from childhood until 28 years in the NFBC 1966 (1). A booster for MS research was a grant from the Finnish Academy in 2003, which enabled to launch Oulu Back Study (OBS), a subpopulation of NFBC 1986 living within 100 km from the city of Oulu. Starting from 2007, 27 publications and four dissertations (2-5) have been published from NFBCs. Two more dissertations will be finished during late 2014.

Along the accomplishment of 46-year data collection in the NFBC 1966, the older birth cohort is in the focus of MS research although ongoing research includes e.g. the effect of clustering of adverse lifestyle and psychosocial factors at 16 years on entering working life in the NFBC 1986.

46-year data in the NFBC 1966 includes objective measurement of pain sensitivity with pain pressure threshold and tolerance, and cold and heat threshold and tolerance. The largest population-based sample allows us to characterize the role of early life events, psychosocial and environmental factors, and work-related issues in pain sensitivity as well as the role of pain sensitivity for future work disability and morbidity.

Other issues of interest in MS research are knee osteoarthritis (OA) and lumbar spine magnetic resonance imaging (MRI) phenotypes and the role of genetics and metabolomics within these phenotypes. Knee radiography has been performed to ca. 1950 subjects enabling to classify cohort members with early knee OA and to investigate a wide spectrum of known and suspected risk factors of OA.

Lumbar MRI has been performed currently to ca. 1000 subjects, and we expect to reach a sample size of 1500 in early autumn. Of lumbar MRI phenotypes, we will focus on intervertebral disc degeneration and the so-called Modic changes, of which the latter is thought to be the most specific degenerative pain-related phenotype.

In the evaluation of genetic factors in MS phenotypes, international collaboration is needed. We have established a consortium consisting of research centers in Asia, Europe and US. Recently, a meta-analysis of GWAS data for lumbar disc degeneration from Hong Kong, mainland China, Japan and NFBC 1966 found an interplay between a polymorphism in the CHST3
(carbohydrate sulfotransferase 3) gene and certain microRNA (6).

MS disorders are associated with many other chronic complex disorders such as e.g. cardiovascular diseases and mental disorders. NFBCs allow us to investigate the etiology of these comorbid conditions. Therefore, in the future collaboration with other research groups of the NFBCs will be our priority in relation to morbidity, mortality and work disability in a life course design from birth onwards.

REFERENCES


Retinal vessels in the Northern Finland Birth Cohort

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INTRODUCTION

For the first time, NFBC cohort will be performed eye examinations with modern imaging tools, in order to investigate the benefits, possible disadvantages and cost-effectiveness of eye screening in glaucoma diagnostics. This gives a unique opportunity to study the retinal vascular parameters and their relationship with pathophysiologic processes in and beyond the retina. Alterations in retinal architecture may reflect early vascular dysfunction, concurrent compensatory mechanisms, and predict later disease. It is likely that retinal vascular changes might be markers of the early preclinical stages of metabolic disorders and might predict the onset of clinical disease. To our knowledge, this is the first population-based birth cohort, in which eye examinations including retinal vessel caliber measurements are performed.

METHODS

Approximately 4000 individuals of the NFBC will have examination visits during the years 2012-2015. Eye examinations will include BCVA, fundus photographs, stereoscopic optic nerve imaging, scanning laser ophthalmoscopy, scanning laser polarimetry, optical coherence tomography, visual fields and a questionnaire. Retinal vessel diameters will be measured and calculated measures will be correlated with previous health variables such as blood pressure, birth weight etc.

OBJECTIVES

1. To investigate the relation of childhood variables (birth weight, gestational weeks, childhood growing, nutritional status, vitamin gain etc.) on retinal vessel caliber and calculated variables (CRAE, CRVE, AVR).
2. To study the relation between retinal vessel diameter and nerve fibre layer thickness, macular thickness in OCT, HRT variables and other eye measurements and prevalence of certain ophthalmic diseases in population-based cohort of healthy adults.
3. To compare retinal vessels diameter (CRAE, CRVE, AVR) to individuals’ present health status related to metabolic syndrome: waist-hip ratio, lipids, hypertension etc.
4. To give estimates of future disease incidence of metabolic syndrome, hypertension, Alzheimer disease etc.
CONCLUSIONS

This is the first population-based birth cohort in which eye investigations with modern imaging tools are included in order to explore the long-term morbidity, intermediate disease markers and symptom variation throughout the life-course. The purpose is to identify high risk groups and biological markers to give tools for early intervention and prevention.

REFERENCES

White matter structure in subjects with familial risk for psychosis – the Oulu brain and mind study

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INTRODUCTION

Friston and Frith (1995)1 suggested that dysfunctional connectivity plays an important role in the pathology of schizophrenia. Diffusion tensor imaging (DTI) studies have found decreased white matter integrity in the frontal and temporal lobes in schizophrenia (Ellison-Wright and Bullmore, 2009)2.

DTI is a magnetic resonance imaging (MRI) method based on water diffusion in tissues yielding information about tissue architecture. The nature of diffusion can be described using indices, such as mean diffusivity which describes the strength of diffusion, and fractional anisotropy which describes the asymmetry of diffusion (Basser and Pierpaoli, 1996)3.

There are few studies evaluating white matter structure in subjects with familial risk for psychosis. In order to determine whether these abnormalities are present in young adults with familial risk for psychosis in the general population, we used DTI to study a population-based birth-cohort sample.

METHODS

We used the Finnish Hospital Discharge Register to detect psychiatric inpatient treatments in parents of the members of the Northern Finland Birth Cohort 1986. We invited subjects with familial risk for psychosis and control subjects to a field study conducted between 2007-2010 when the subjects were aged 20-25 years. During the study DTI, cognitive test battery, and background questionnaires were completed4.

We used DTI and tract-based spatial statistics (TBSS) to compare fractional anisotropy, mean diffusivity, and axial and radial diffusion of 47 individuals (17 males) with familial risk for psychosis and 51 controls (17 males). We separately analysed subjects with familial risk for schizophrenia (N=13) and compared to 13 gender-matched controls.

RESULTS

Groups were comparable regarding demographic variables such gender, age, handedness and educational level (Table1). We found no significant difference between groups in intelligence, Global Assessment of Functioning (GAF) or alcohol use.

There were no statistically significant differences between the groups in any of the DTI measures.
Table 1  Demographics in the familial risk for psychosis and Control groups in the Oulu Brain and Mind Study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Familial risk group (n = 47)</th>
<th>Control group (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years [M (SD)]</td>
<td>22.3 (0.8)</td>
<td>22.2 (0.7)</td>
</tr>
<tr>
<td>Gender, male [N (%)]</td>
<td>17 (36)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Handedness, right [N (%)]</td>
<td>44 (94)</td>
<td>50 (98)</td>
</tr>
<tr>
<td>Education level [N (%)]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 9 school years</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Comprehensive</td>
<td>19 (40)</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Matriculation</td>
<td>27 (57)</td>
<td>36 (71)</td>
</tr>
</tbody>
</table>

M = mean, SD = standard deviation

CONCLUSIONS

Contrary to our expectations we did not find differences in white matter structure between familial risk and control groups. This suggests that white matter abnormalities may not be a genetic feature for risk of psychosis and preceding onset of psychosis. Our findings do not support the theory of disconnectivity as a primary sign of psychosis in the brain in young adults.

REFERENCES


Lifelong trajectories of self-determined and measured physical activity and sedentary behavior

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INTRODUCTION

Evidence-based planning of public health interventions requires knowledge on lifelong trajectories for physical activity (PA) and inactivity as well as on their associations with subjective well-being. Current physical activity guidelines are primarily based on observational studies with PA being assessed via self-report. However, there appears to be disparity between self-reported and objectively measured PA.

AIMS

The aims of this study are:

1) to analyze and model the determinants and lifelong trajectories of PA and sedentary behavior,
2) to evaluate changes and their determinants in PA behavior and fitness as well as changes in wellbeing from the age of 31 to the age of 46 and
3) to examine how the changes in PA behavior and physical fitness from the age of 31 to 46 years affect health, social factors, lifestyle and wellbeing.

METHODS

The study population consists of the Northern Finland Birth Cohort (NFBC 1966) which is a longitudinal one-year birth cohort originally including all those born in 1966 in Northern Finland (N=12 058). The members have been monitored prospectively from the prenatal period onwards.

At the age of 46 years a health examination was conducted (N=5 852). PA behavior and time spent sitting was measured using Polar Active (Polar Electro, Finland) and Hookie AM20 (Traxmeet, Finland) for 14 days (Fig. 1). Self-reported PA has been acquired via questionnaires at 14, 31 and 46 years, and sedentary behavior at 46 years.

Key determinants studied in relation with PA lifestyle include academic achievement, grades, measured cardiorespiratory and muscular fitness, weight, smoking, alcohol use, diet, sleep, sociodemographics, life satisfaction, personality and temperament.
Figure 1. Polar Active (top) and Hookie AM20 (below) devices for measurement of physical activity.

RESULTS

The results will show how physically active or inactive lifestyle is developed and what are the determinants of PA and sedentary behavior and its impact on subjective wellbeing.

CONCLUSIONS

This study will generate new, evidence-based knowledge for promotion of PA and prevention of sedentary behavior at population level.

REFERENCES

Local residential area and health of young adults - a Northern Finland Birth Cohort 1966 study.

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INTRODUCTION

Sparsely populated Finland is an interesting area for studying the effects of population density and geographical distance on health. Previous studies indicate many health problems in rural and remote areas. We have studied the importance of local residential area to health of young adults: how residential area is associated with health, what the role of geographical distance is and how health is associated with moving in different areas.

METHODS

We have utilized the 31-year follow-up data from the Northern Finland Birth cohort 1966 study, originally including all children who were born in the provinces of Oulu and Lapland in Finland in 1966. Local residential area has been defined with 1 km² population density grid data, and distances to municipality center or health center has been calculated using Finnish road network data (Digiroad). We have used the ordinal logistic regression for studying the perceived health in rural and urban areas, generalized additive model for studying the body mass index (BMI) and overweight in relation to distance to community center and population density in local residential area, negative binomial regressions and concentration indices for examining the role of distance in health center use, and multinomial logistic regressions for studying the health’s association with moving in rural and urban areas.

RESULTS

The poor perceived health was found to increase from densely to sparsely populated areas; among rural men the adverse lifestyle and psychosocial factors explained these associations, while among women reasons for poor health in scattered settlement areas remained unclear (1). BMI and prevalence of overweight were found to increase from distances greater than 5 km from community center and with decreasing population density (2). Distance to health center was not
found to be an important barrier in health center use among young adults. Poor health was associated with moving; dissatisfaction with life and lifetime morbidity being associated with rural-urban moves, activity limiting illness with rural-rural moves, and frequent use of health services with all urban moves (3).

CONCLUSIONS

Geographical distance to health center was not an important factor in service use among 31-year old young adults. However, local health inequalities within administrative areas were identified with grid-based data. Also indication that urban sprawl may affect people’s bodyweight was found. These denote the importance of residential area to health and urge the health-based planning of residential areas. Also, Individual’s health status was associated with moving, which may have implications for rural-urban health inequalities, also in local level.

REFERENCES

Metabolic syndrome in young adults born preterm - the ESTER study

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INTRODUCTION

Children and adults born as small/early preterms have increased levels of components of the metabolic syndrome such as elevated blood pressure1 and insulin resistance2. Whether this applies to those born less preterm, representing majority of prematurity, is poorly known. We studied the association of preterm birth across its whole spectrum with hypertension, obesity and metabolic syndrome in young adults.

METHODS

This study was part of the ESTER study (2009-2011), in which we studied the health of young adults born preterm. The perinatal data of the participants recruited through the Northern Finland Birth Cohort 1986 (NFBC 1986, born in 1985–1986) came from the cohort database. We collected corresponding data for those invited through the Finnish Medical Birth Register (FMBR, born in 1987–1989) from hospital and maternal welfare clinic records. This study included 134 participants born at <34 gestational weeks (early preterm), 242 born at 34–36 weeks (late preterm) and 344 born at ≥37 weeks (controls). At the mean age of 23.2 years they participated in a clinical examination, with blood pressure and anthropometric measurements, and blood tests including plasma lipids.

RESULTS

Adults born preterm were two- to three-fold more likely have hypertension (systolic blood pressure ≥140 mmHg, diastolic ≥ 90 mmHg) (Figure1). Those born preterm were also approximately two-fold more likely to be obese (BMI > 30 kg/m2). In addition, metabolic syndrome according to the Joint Interim Task Force Criteria was more common in preterm groups and they were more likely to have an intermediate or high (>30) fatty liver index, a proxy of non-alcoholic fatty liver disease.
CONCLUSIONS

We found that young adults born preterm are at higher risk for developing hypertension, obesity, metabolic syndrome and increased fatty liver index, a predictor of non-alcoholic fatty liver disease than their peers born at term. These risks are increased also in those born late preterm – in the group representing the majority of preterms.

REFERENCES

Design options in cohort studies: Sampling-based alternatives to a census of the study population

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INTRODUCTION
Paula Rantakallio recognized the need to have a large, population-based cohort of parturients and offspring in etiological studies on various perinatal and pediatric outcomes. Moreover, she realized that when it was too costly and laborious to collect data on certain risk factors for all members of the cohort, then selective data collection using sampling stratified by key outcomes was a reasonable approach.

In this presentation recent methodological advances in outcome-selective sampling designs, collectively known as case-control studies, are briefly reviewed and their application in birth cohort studies is illustrated.

OBSTETRIC DATA IN 1966
In NFBC 1966, data on selected maternal and fetal risk indicators, including diabetes, hypertension, anaemia, vaginal bleeding, complications in placenta, and malformation in the offspring, were collected from available pre- and perinatal records according to an elaborate sampling plan. In this scheme the aim was to cover all “cases”, i.e. offspring with at least one of the following outcomes: low birth weight, preterm birth, post-term birth, stillbirth and neonatal death. The “control” group comprised a random sample drawn with only a ten percent sampling fraction of those having none of the outcomes above.

STUDY POPULATION AND STUDY BASE
Classification of study designs is here based on concepts of study population, study base, and sampling strategy.

The study population is either a closed population i.e. a cohort, or an open or dynamic population. Birth cohort is a prime example of a closed population. In contrast, a typical open or dynamic population is the catchment population of a hospital or a disease register over a time period, utilized in hospital- or register-based case-control studies.

The study base consists of the experience of the study population in time. It is cross-sectional or longitudinal depending on whether the prevalence or incidence of the outcome is considered.

In birth cohort studies the study base is cross-sectional as to health states at given time points, e.g. low weight or a malformation at birth, or some chronic condition at 31 years. In a longitudinal base, events or changes of health state during specified periods are considered, like getting diabetes in childhood, or myocardial infarction in adulthood.

FULL COHORT DESIGN
Sampling strategy refers to the principle for collecting risk factor data from the study cohort. A straightforward first option is a census of the whole study base, i.e. the full cohort design.

Census was performed in NFBC 1966 as to the questionnaire data. The questionnaires were filled and utilized in statistical analyses for all those over 12,000 mothers belonging to the cohort.

Full cohort design is costly and laborious in big cohorts, in particular for measurements of risk factors from e.g. blood samples or dietary diaries.
SAMPLING FROM COHORT

An alternative general strategy to census is outcome-selective sampling. The main options are (A) case-noncase sampling, i.e. the traditional or “textbook” case-control study, (B) case-cohort sampling, and (C) density sampling.

In the case-noncase design (A) the controls are randomly sampled from those remaining free from outcome at the end of relevant risk period. This design is extensively used in studies of congenital malformations with a cross-sectional base and prevalent cases. It is common in studies on disease outbreaks, too, in which the study base is longitudinal with incident cases occurring in a fairly short risk period. The odds ratios are the only comparative parameters that are directly estimable from such case-control data.

Collection of obstetric data in NFBC 1966 was a complex extension of this design principle, covering both cross-sectional and longitudinal outcomes.

The case-cohort design (B) is based on selecting the group of controls, or subcohort, as a random sample of the whole cohort. Thus, some of the cases may be included in the subcohort, too. This causes no methodological problem, because the role of the controls here is to represent the distribution of risk factors in the whole cohort or study base. From appropriately sampled case-cohort data valid estimates are directly obtained for the ratios of prevalences, incidence proportions, or rates, respectively.

Case-cohort design has gained popularity in studies on chronic diseases. It has also been applied for congenital malformations or pediatric outcomes. A major advantage of it is that the same subcohort can easily be utilized to serve as the control group for various types of cases, if several outcomes are aimed to be addressed in the same cohort.

The density sampling design (C) is applicable only in a longitudinal study base. Its main variant, nested case-control study, is typically used in a cohort setting. For each new case that emerges during follow-up, one or more control subjects are randomly chosen from the risk-set, i.e. those members of the study population who are still alive and free from outcome at the time of diagnosis of their case.

The nested design is nowadays the most popular sampling scheme from a cohort in studies on chronic diseases. It allows direct estimation of the incidence rate ratios between exposure groups.

In designs (A) and (C) one may increase statistical efficiency by matching on a few important determinants of the outcome. In studies involving biomarkers as risk factors, additional matching on storage-time, freeze-thaw cycles and analytic batch in the nested design improves comparability of measurement between cases and controls. This is an advantage compared to the case-cohort design. However, the latter may be preferable in situations where sufficient stability of biomarkers is expected.

These three main sampling schemes have largely similar statistical efficiency. Moreover, the same broad framework for statistical modelling, logistic regression, unconditional or conditional when appropriate, can be applied in data analysis.

CONCLUSION

The notion of case-control study is not a single entity but encompasses a diversity of design options for addressing various research questions in birth cohort studies in a cost-efficient manner, such that the essential statistical information contained in a large cohort is optimally extracted.
Patterns of early growth and metabolic phenotypes in adult life

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The aim of this project is to investigate if early growth patterns are predictive of metabolic phenotypes in adulthood in a population-based setting. Our group has extensive experience in analyzing NMR metabolomics data such as those available in the NFBC. Simultaneously, we have developed sophisticated computational tools to integrate complex clinical data with the metabolic profiles that characterize the diversity within a given population. In this project, we plan to integrate the information on early growth with the metabolic data, and obtain a systems-wide view on their longitudinal connections. We expect that this approach has the power to detect distinctive subpopulations of children at higher risk for metabolic dysfunction in adulthood, which in turn is a risk factor for diabetes and cardiovascular disease later in life.
Polycystic ovary syndrome: what have we learned from the cohort studies?

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder suffered by 5-10% of women in reproductive age and characterised by oligomenorrhea or amenorrhea, hyperandrogenism, hirsutism, and polycystic ovaries at ultrasound (1). Insulin resistance and obesity are also common symptoms among PCOS-symptomatic women, which later in life expose them to type 2 diabetes mellitus (T2DM), metabolic syndrome and cardiovascular morbidity. The most common clinical symptoms related to PCOS are menstrual disturbances and infertility related to anovulation, but there are only few follow-up studies investigating the effects of PCOS on reproductive performance and pregnancy complications. Moreover, most studies are unable to distinguish the respective roles of PCOS per se and obesity as causal factors for metabolic and gestational risks.

METHODS

The projects use both the Northern Finland Birth Cohort 1966 (NFBC66) and the Northern Finland Birth Cohort 1986 (NFBC86).

In the NFBC66 we use the two questions on hirsutism and oligo-amenorrhea included in the questionnaire at age 31: 1) Is your menstruation cycle over twice a year more than 35 days? and 2) do you have excessive body hair? Of the women who returned the questionnaire, 24.6% reported symptoms of hirsutism and/or oligo-amenorrhea, 10.6% reported hirsutism alone, 10.5% oligo-amenorrhea alone and 3.5% (N=153) reported both symptoms. The reference group includes all other women of the cohort without any PCOS symptoms (N=3340).

In the projects ongoing, we use the data of the questionnaire and of the clinical examination performed at age 46.

In the NFBC86 we use the answers to the questionnaire at age of 16 years including one question on the regularity of the menses, and the results of the metabolic and hormonal investigations. We sent a follow-up questionnaire in 2012 at age 26 about reproduction, menstruation and infertility. Overall 2270 (49.7%) women responded to this last questionnaire. After combining the 16- and 26-year follow-up questionnaires, the final study sample includes 2033 singleton females.

RESULTS

In the NFBC66, we could show that at age 31 self-reported oligomenorrhea and hirsutism can distinguish most women with the typical endocrine and metabolic profile of PCOS (2,3): the women with self-reported symptoms of oligo-amenorrhea and hirsutism were more obese, hyperandrogenic and insulin resistant compared to healthy women. Women with PCOS symptoms had at age 31 lower fecundability and suffered more often from infertility, but had at least one delivery as often as non-symptomatic women. Against earlier hypotheses, women with PCOS did not exhibit an increased risk of spontaneous abortion (4). These results were confirmed in a later follow-up study in this same cohort performed at age 44, indicating that
women with symptoms of PCOS had their first child at the same age and were not more often childless when compared with non-symptomatic women (5). The impact of symptoms of PCOS on fertility and family size was limited, suggesting that women with PCOS from infertility clinics represent a more severe phenotype than those from the general population. These results are also important clinically, showing that fertility can be restored, at least partly, by infertility treatments. At the end of their reproductive age, however, women with symptoms of PCOS did not quite match the parity of healthy non-symptomatic women. (5)

Future plans aim to investigate the respective roles of symptoms of PCOS and obesity on pregnancy complications, such as gestational diabetes (GDM), pre-eclampsia (PE) and pregnancy induced hypertension (PIH), and newborn’s health are ongoing.

In addition, projects on the NFBC66 have been started to investigate the effects of obesity, weight gain from birth to the age of 46, way of life (physical activity, nutrition and smoking) on the evolution of the syndrome and the development of metabolic risks, such as T2DM and cardiovascular risks.

In the NFBC 86, we could show that oligo/amenorrhea, enquired about via a simple question at the time of adolescence, is a good marker of hyperandrogenaemia and may be a risk factor for the development of PCOS in adulthood. Our findings confirmed that the association between oligo/amenorrhea, hyperandrogenism, obesity and metabolic risks is already evident in adolescence, which strengthens the importance of noting menstrual disorders at an early stage. (6) We also showed in the NFBC66 that obesity in adolescence and in adulthood, and also weight gain after adolescence, are associated with self-reported PCOS symptoms in adulthood (7).

CONCLUSIONS

Our study populations give us a unique opportunity to follow the women with symptoms of PCOS from birth to late adulthood and to investigate the effects of obesity, weight gain, way of life (physical activity, nutrition and smoking) on the evolution of the syndrome and the development of metabolic and reproductive risks. These projects will also allow us to determine the targets of preventive actions to minimize the early and late health risks related to PCOS.

REFERENCES

Response initiation in young adults at risk for psychosis in the NFBC-1986

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INTRODUCTION

This is one of very few studies to investigate the specific executive function/processing speed component of response initiation in subjects at familial risk for psychosis, and the first such study in subjects at clinical risk for psychosis.

METHODS

Participants (N=177) were members of the general population based Northern Finland 1986 Birth Cohort in the following four groups: familial risk for psychosis (n=62), clinical risk for psychosis (n=21), psychosis (n=25) and control subjects (n=69). The response initiation of these groups was compared in three different tests: Semantic fluency, Stockings of Cambridge and Spatial working memory.

RESULTS

The two risk groups did not differ significantly from control group, but differed from, and outperformed the psychosis group in semantic fluency response initiation.

CONCLUSIONS

Response initiation deficits were not evident in a non-help seeking psychosis high-risk sample.
Offspring of antenatally depressed mothers – the Northern Finland 1966 Birth Cohort

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INTRODUCTION

Depression is common, also during pregnancy. To our knowledge, only in the Northern Finland 1966 Birth Cohort (NFBC 1966) there have been long follow-up reports of the mental and behavioural problems in the offspring of antenatally depressed mothers later on in adulthood. Previously in the NFBC 1966 the risks for schizophrenia and other psychoses have been found to be elevated in the offspring of antenatally depressed mothers only with parental psychosis. In the NFBC 1966 maternal depressed mood during pregnancy has also been associated with criminality in males, but not with risk for suicides, pain-related temporomandibular disorder symptoms nor lower levels of attained education in the offspring. Now our aim was to study severe depression and other hospital treated mental disorders in the offspring of antenatally depressed mothers, when taking account parental mental disorder.

METHODS

In the NFBC 1966, mothers of 12,058 children were asked at mid-gestation at the antenatal clinic if they felt depressed. The offspring were followed for over 40 years till 2008. Subsequent severe, hospital treated mental disorders in the offspring were detected using the Finnish Hospital Discharge Register, which was also used for identifying mental disorders in the parents till 1984, when the offspring were of age.

RESULTS

Of the offspring of antenatally depressed mothers 3.0% and 1.9% of the other cohort members had had severe in-patient treated depression during the follow-up. Maternal depressed mood during pregnancy increased slightly the risk for hospital-treated depression in the offspring (crude OR 1.6; 95% CI 1.1-2.2). Maternal depressed mood during pregnancy combined with parental hospital-treated mental disorder increased the risk for severe hospital-treated mental disorders among the offspring widely: the risk was increased for depression (3.5; 1.9-6.2), bipolar disorders (7.2; 2.5-21.1), schizophrenia (4.3; 2.3-8.2) and substance misuse (2.8; 1.7-4.7), when compared with the offspring without antenatally depressed mother and without parental hospital-treated mental disorder. These risks were also higher than in the offspring without maternal antenatal depression and with parental mental disorder.

CONCLUSIONS

Maternal depressed mood during pregnancy increased the risk for severe depression in the offspring slightly when compared with the children of mothers without antenatal depression, but had a
stronger effect on subjects at risk of severe mental disorder due to familial history. Maternal depressed mood during pregnancy combined with parental hospital-treated mental disorder increased the risk not only for depression but for other severe hospital-treated mental disorders in the offspring, too. Antenatal depression may act as an adverse environmental factor in those with genetic vulnerability.

REFERENCES


Childhood and adolescence symptoms preceding first episode psychosis in the Northern Finland 1986 Birth Cohort

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INTRODUCTION

The onset for psychotic disorder is often in adolescence. At least some of them are considered to be neurodevelopmental disorders. Prospective general population based reports are lacking on specific symptoms in childhood and adolescence predicting clinically treated first episode psychosis in youth and having as a control group also non-psychotic psychiatric cases, and in this way taking account specificity.

We wanted to describe which kind of symptoms precede onset of psychosis when taking account specificity.

METHODS

Members of the Northern Finland 1986 Birth Cohort, an unselected general population based cohort, were examined in childhood (N=8258) and adolescence (N=6514). The 8–year field study included Rutter B2 questionnaire for teachers and subscales from Rutter A questionnaire for parents screening antisocial and neurotic symptoms. The 15–year field study included a 21-item PROD-screen questionnaire screening prodromal symptoms for last six months. The Finnish Hospital Discharge Register was used to find out new cases of psychosis and non-psychotic mental disorders till the age of 23 years.

RESULTS

High scores of antisocial and neurotic symptoms in Rutter B2 and in subscales of Rutter A did not associate with later psychosis. The highest prevalence of positive symptoms in the PROD-screen were in the group of adolescents who developed psychotic disorder (65% over the cut off) compared to group of subjects who developed hospital-treated non-psychotic disorder (36%, p<0.001), and to group of subjects without any disorder (27%, p<0.001). Respective figures for negative symptoms were 55% in the
group of psychotic adolescents, 30% in the group of subjects with non-psychotic disorder (p=0.01) and 24% in the ‘healthy’ (p<0.001).

**CONCLUSIONS**

Antisocial and neurotic symptoms reported by teachers and parents at age 8 did not predict psychosis. Both positive and negative features were common in adolescents, especially in those who later developed psychosis. In this large prospective population sample both positive and negative symptoms in adolescence associated specifically with development of first episode psychosis.

**REFERENCES**


Intergenerational and long-term consequences of pregnancy disorders and chronic diseases on cardiovascular disease and dementia

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INTRODUCTION

Parental history of cardiovascular diseases, hypertension, and diabetes is associated with increased risk of hypertension or preeclampsia, a pregnancy-specific new-onset hypertensive disorder with proteinuria, in the daughter.$^{1-3}$ Offspring exposed in utero to maternal hypertensive disorders have poorer metabolic risk profile in adolescence and a higher risk of preeclampsia.$^{4-6}$

Hypertension is a known risk factor for lower cognitive function and dementia and the adverse effects of hypertension on white matter disease and brain infarctions have been shown to begin early.$^{7,8}$ Even transient hypertension in pregnancy increases risk of ischemic heart disease and stroke—generally with a risk comparable to those with chronic hypertension in pregnancy.$^{9}$

The objectives of the study are 1) to determine the effects of parental life-course history of chronic diseases and in utero exposure to maternal hypertension on the risk of hypertensive disorders of pregnancy and on cardiovascular risk factors in the adult offspring; 2) to determine if hypertension during pregnancy increases risk of dementia; and 3) to determine if paternal chronic diseases diagnosed before or during pregnancy are associated with pregnancy complications.

METHODS

Previously collected data from the prospective Northern Finland Birth Cohort 1966 (NFBC 1966) as well as Finnish register-based health and demographic data will be used to answer these research questions. Data from the index pregnancy of NFBC 1966 (N=12055 women, N=12068 deliveries) as obtained from the antenatal cards or via a cohort questionnaire will serve as base maternal and in utero exposure data. This data includes the routine blood pressure measurements and urinary tests for protein in 1966 (complete data available for 87.1% of the population) used to categorize women as normotensive (no blood pressure elevation during pregnancy, no proteinuria) or as having hypertensive disorders of pregnancy.$^{9}$

Register-based data will include data on parental life-course diseases (including dementia) from the Special Reimbursement Entitlement Register, the Hospital Discharge Register and the Register of Causes of Death. Data on the own children and pregnancies of subjects of NFBC 1966 will be collected from the Medical Birth Registry (from 1987 onwards), which includes key pregnancy, perinatal and newborn data on all live- and stillborn infants $\geq$22 weeks’ gestation or with birth weight $\geq$500 grams. Data on diseases during pregnancy will be supplemented using the Hospital Discharge Register.
Data on cardiovascular health of the NFBC 1966 subjects will be obtained from the clinical examination and postal questionnaire at age 31 years and 45 years (with respective response rates of 71.3% and 77.4%). The clinical examination included measurements of weight, height, hip and waist circumference, blood pressure measurements, lung function and grip strength, as well as analyses for blood counts, lipids, fasting glucose and insulin.

RESULTS
The study is still under data collection and we have no publishable results yet. We have previously shown that hypertensive disorders of pregnancy are important predictors for clustering of cardiovascular risk factors, and increase the risk of cardiovascular diseases, strokes, diabetes, and chronic kidney disease during the life-course. Hypertensive disorders are also a significant cause of neonatal morbidity. Hence, identification of early-life risk factors might be important when trying to identify at-risk individuals for hypertensive disorders and chronic diseases during the life-course.

CONCLUSIONS
This study will address an important clinical issue – can pregnancy or in utero information be used to identify high risk individuals for cardiovascular diseases, other chronic disease and pregnancy complications in offspring as well as in mothers. The novelty and significance of this study is based on unique data sets with prospectively collected data on in utero exposures and register-based data on health outcomes.

REFERENCES
Work related stressors and obesity in the Northern Finland Birth Cohort 1966

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INTRODUCTION

Obesity is associated with a cluster of cardio-metabolic disorders. However, a significant proportion of obese individuals does not develop these obesity-related complications and appear metabolically healthy, which leads to the concept of Healthy Obesity ¹,². The increased rate of obesity from 25 to 45 years old in the population coincides with the entry into the working life and the foundation of a career. Numerous subsequent factors of biological and psychological stress from and outside work are susceptible to affect the individual during that period ³. Connections between stress and inflammation have been shown, increasing evidence for a link between inflammation and metabolic disorders associated to obesity is observed ⁴. The aim of this study is to demonstrate the biological underlying mechanisms (inflammation, genetic regulation) linking the work-related stressors and the risk of unhealthy phenotype in obesity and other components of metabolic syndrome in the general population.

METHODS

The study population is the Northern Finland Birth Cohort 1966 (NFBC1966). The members are all men and women born in 1966 in the two northernmost provinces of Finland, Oulu and Lapland (N=12058). Individuals were followed-up from birth by questionnaires and clinical examinations at 31 and 46 years of age. In addition, the characteristic variables for the working population of the NFBC1966 are identified by linkage with the register data of Finnish Centre for Pensions. Our study population comprises 5171 individuals (49.80% male). Analyses were carried out with the SAS statistical software V.9.3 (SAS Institute Inc, Cary, NC, USA) using ANOVA to analyze continuous outcomes and Xi² for categorical outcomes.

RESULTS

According to Wildman’s classification ¹, we identified a sub-population with healthy cardio-metabolic phenotype among the obese individuals in the NFBC1966 population, i.e. Healthy Obese (HO). When compared with normal weight individuals, the prevalence of unhealthy cardio-metabolic phenotype is higher in overweight obese individuals, irrespective of the sex (Figure 1 and 2). In the normal weight category we found that 18.7% of men and 9.1% of women were presenting an unhealthy phenotype whereas in the obese category, 25.1% of men and 37.3% of women display a healthy cardio-metabolic phenotype.
Figure 1. Prevalence of healthy and unhealthy cardio-metabolic phenotype according to BMI in men in NFBC1966.
Light color: healthy cardio-metabolic phenotype and dark color: unhealthy cardio-metabolic phenotype.

Figure 2. Prevalence of healthy and unhealthy cardio-metabolic phenotype according to BMI in women in NFBC1966.
Light color: healthy cardio-metabolic phenotype and dark color: unhealthy cardio-metabolic phenotype.

REFERENCES


Lifetime health behaviors and work ability in midlife: 
a prospective cohort study

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INTRODUCTION

Very little evidence exists of the cumulative and longitudinal effects of health behaviors on work ability (WA). We investigated the cumulative effects of lifetime (14–46y) health behaviors on WA at the age of 46.

METHODS

The study population included 46-year-old men and women (n~2800), born in Northern Finland in 1966. Data on their current perceived WA compared to lifetime best (scale 0 to 10; first item of Work Ability Index), and health behaviors (leisure time physical activity, smoking and alcohol consumption) were assessed through questionnaires. Health trajectories were created on the basis of health behaviors at the ages of 14, 31 and 46. Stress-related eating at the age of 31 was also assessed.

Analysis of covariance was used to investigate the effects of health trajectories and stress-related eating and drinking on WA at 46. The analyses were controlled for basic education, physical strenuousness of work, sedentary work, job stress, and BMI at the age of 31.

RESULTS

Four health trajectories were created; always healthy, change from healthy to average health, change from healthy to unhealthy, and always unhealthy. Those who belonged to the healthy to unhealthy and always unhealthy trajectories had lower levels of WA compared to those with the always healthy trajectory, among both genders. After adjusting for covariates, stress-related eating and drinking had no effect on WA.

CONCLUSIONS

Lifetime unhealthy behaviors increase the risk of poorer WA in midlife.

The study was funded by the Finnish Work Environment Fund (111252)
REFERENCES


Obesity and work ability in midlife: a prospective cohort study

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INTRODUCTION

There is little evidence concerning the longitudinal associations between obesity, weight change and work ability (WA)¹. We investigated the effect of obesity at 31 years and weight change between 31 and 46 years on WA at 46.

METHODS

The study population included 46-year-old men (n=2598) and women (n=2945), born in Northern Finland in 1966. Data on their current perceived WA compared to lifetime best (scale 0 to 10; first item of Work Ability Index) was assessed through questionnaires at the age of 46. Weight (kg) and height (cm) were measured at 31 years. At the age of 46, weight and height were self-reported. Analyses of covariance were used to investigate the effect of BMI class [normal weight (BMI <25.0kg/m²), overweight (BMI 25.0-29.9) and obese (BMI ≥30.0)] on WA at 46. Weight change between 31 and 46 years was classified into two groups: 1) BMI ≤29.9 at both ages and 2) BMI ≥30 at both ages or BMI increased from ≤29.9 to ≥30. Basic educations, physical strenuousness of work, sedentary work, job stress, parity, and BMI at the age of 14 or 31 were controlled for in the analyses.

RESULTS

Nearly all participants gained weight between the ages of 31 and 46. Among men, overweight and obesity at 31y, and among women, obesity at 31y predicted lower WA at 46y. Weight gain and being obese at both ages significantly decreased WA at 46y among both genders.

CONCLUSIONS

Obesity and weight gain increase the risk of deteriorated work ability in midlife. The study was funded by the Finnish Work Environment Fund (111252)

REFERENCES

The effects of structural genomic variations on human phenotype

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INTRODUCTION

The total number of bases that can be affected by genomic structural variations (GSVs) is much higher than the number of bases affected by single nucleotide polymorphisms (SNPs)¹. We aim to identify GSVs including both copy number variations (CNVs) and inversions in the human genome, and determine the implications of those variants on particular human phenotypes. We initially concentrated on identifying candidate CNVs associated with obesity-related phenotypes such as body mass index (BMI) in the two Northern Finland Birth cohort datasets (NFBC1986 and NFBC1966).

METHODS

Detailed clinical data and whole blood samples were obtained at 16 (NFBC1986) and 31 years old (NFBC1966) and genomic DNA was prepared from the blood. Genome-wide genotyping data from a total of 2,016 subjects from NFBC1986 and 1,536 subjects from NFBC1966 has been used to identify predicted CNVs, following quality control (QC). Subjects that did not satisfy one of the QC criteria were excluded. The remaining subjects were adjusted for population structure, inbreeding status and relatedness. Clear population and ethnic outliers were excluded from analysis. CNV scans on coding regions were performed by PennCNV² software.

RESULTS

More than 90% of the subjects from each cohort passed all QCs and the stringent CNV QCs in the primary detection stage by PennCNV. Both cohorts were distinctive and highly homogenous compared to European, African and Asian populations. To date, we have identified 6,150 and 7,767 predicted CNVs that affect coding regions, in NFBC1986 and NFBC1966 respectively.

CONCLUSIONS

CNV predictions using a secondary CNV calling algorithm are now required to validate the CNVs identified in both cohorts. Statistical tests will be performed to identify CNVs associated with various phenotypes, including BMI. CNVs associated with any phenotypes will be experimentally validated and characterised in detail.

REFERENCES

Predisposing factors and consequences of disruptive behavioral disorders and ADHD in the NFBC 1986

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INTRODUCTION

Disruptive Behavior Disorders (DBD) and Attention Deficit Hyperactivity Disorder (ADHD) are common and often co-occurring psychiatric disorders among children and adolescents. DBD consists of two behavioral disorders: conduct disorder (CD) and oppositional defiant disorder (ODD). This study concentrated on these disorders and the possible predisposing factors and consequences of them.

This study had been implemented in three parts. The first part examined the early risk factor of DBD and/or ADHD, seeking the possible reasons and the ways of preventing these disorders. The second part described the current well-being of the adolescent with one or both of these disorders, the severity of behavioral problems and school performance. The third part evaluated the general psychiatric morbidity of these adolescents.

METHODS

The study sample (N=457) is based on the Northern Finland Birth Cohort 1986 (NFBC 1986). The adolescents in the sample participated into the ADHD research in 2001 (1). Based on that research, the sample divided into four groups: adolescents with DBD (n=44), ADHD (n=91), comorbid DBD & ADHD (n=91) and without either disorder (n=250).

This study compiled various data sources in different time points available in NFBC 1986. The possible risk factors preceding DBD and/or ADHD were obtained from the questionnaires completed by the children’s parents during pregnancy and childhood. The variables describing the severity of behavioral problems and current wellbeing of the adolescents were obtained from clinical examination (ADHD research) and the Finnish National Board of Education (school grades at the end of 9th grade). The information about psychiatric morbidity was obtained from the Finnish Hospital Discharge Register.

All statistical analyses were completed using SAS 9.3, R 3.0.1 or IBM SPSS Statistics 21. The data was evaluated e.g. through contingency tables, analysis of variance, multinomial logistic regression analysis, factor analysis, survival analysis and structural equation modeling.
RESULTS

In the first part of our study, we found out that different risk factors were associated with different study groups. For example, female gender and paternal admittance into the psychiatric care were associated with DBD. Childhood hyperactivity was associated with ADHD and childhood hyperactivity and scholastic impairment with comorbid DBD & ADHD.

While studying the severity of behavioral problems and school performance, we found that the behavioral problems were the most severe in the comorbid DBD & ADHD group and their school performance was the poorest.

![Figure 1](image.png)

**Figure 1.** The occurrence of other psychiatric disorders in study groups (2).

In the third part of our study, we found out that the psychiatric morbidity seemed to associate with DBD; adolescents diagnosed with DBD (with and without ADHD) were at high risk undergoing psychiatric hospitalization during their life. Figure 1 presents the cumulative incidence of the first occurrence of psychiatric disorder in FHDR among our study groups, obtained via a Kaplan-Meier analysis.

CONCLUSIONS

Different risk factors affect into the different behavioral problem, the type of the behavioral problem should be taken into account while trying to prevent these disorders. The adolescent with both DBD and ADHD has the severest behavioral problems and performs the worst in school which can be seen already in the childhood. An adolescent with DBD is also in risk of developing other psychiatric disorders.

REFERENCES


Determinants of vitamin D status in healthy population at 31 years in the Northern Finland Birth Cohort (NFBC)-1966

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INTRODUCTION

Vitamin D deficiency is an emerging risk factor for various disease conditions. Vitamin D deficiency is determined by serum 25-hydroxyvitamin D (25(OH)D) concentrations\textsuperscript{1,2}. The primary determinant of vitamin D status is the exposure to UV-B rays\textsuperscript{3}. The other population determinants of vitamin D status are season variability, latitude, time of the day, use of sunscreen, climate variations, cultural practices, age and skin colour\textsuperscript{4}. The prevalence of vitamin D deficiency and the associated determinants in the 65ºN remain unclear. The purpose of the study is to estimate the prevalence of vitamin D deficiency and the factors related to low serum 25(OH)D levels in the Northern Finland Birth Cohort (NFBC) 1966.

METHODS

The study is a follow-up of the NFBC 1966. All mothers who were living in the two northern most provinces of Finland, Oulu and Lapland were enrolled in the study and were expected to have their delivery dates in 1966: Over 96% participated (12,055 mothers with N=12,058 live born children) during 1\textsuperscript{st} January and 31\textsuperscript{st} December 1966. The follow-up data collections were conducted at 1y, 14y, 31y and recently at 46 years (due to finish in February 2014). At 31 years, the clinical examination data are of N= 6033 (71.3% of eligible, i.e. those still living in the provinces of Oulu and Lapland and in Helsinki area). The serum vitamin D measurements at 31 years are available in N=5659. Serum 25(OH)D levels ranged from 6 nmol/l to 141 nmol/l in NFBC-1966.

RESULTS

The mean and median serum 25(OH) D levels were 50.5 nmol/l and 49.8 nmol/l. Serum 25(OH)D in the study population showed a relatively normal distribution (figure 1).

The preliminary analysis of the study has shown seasonal specific variations with the vitamin D concentration (figure 2). Further analysis of the study population will reveal the exact prevalence of vitamin D deficiency in the NFBC-1966.
Figure 1. Distribution of 25(OH)D in NFBC1966 (N=4366).

Figure 2. Season of blood drawn and vitamin D concentration in the NFBC-1966 stratified for sex.

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Population isolates provide a special opportunity to study the contribution of low frequency and rare variants in human traits. The enrichment of rare, Mendelian, mostly recessive diseases in population isolates is well documented and widely studied. The unique population of Finland is one of the prime examples of long lasting isolation and multiple population bottle necks resulting in the enrichment of some 36, mostly recessive, diseases that are extremely rare in other Caucasian populations. The new opportunities for large scale sequencing have stimulated investigators around the world to focus on identification of low frequency variants enriched in the Finnish population. This collaborative sequencing project SISu (Sequencing Initiative Suomi combines the effort of the Broad Institute, University of Michigan, UCLA, University of Oxford, University of Lund, Wellcome Trust Sanger Institute, Finnish Institute of Molecular Medicine (FIMM), University of Eastern Finland and The National Institute for Health and Welfare, Finland. We currently have whole exome or low coverage whole genoma sequence data from about 8000 Finns. Currently whole genome or whole exome sequencing is in progress for tens of thousands of Finns. This provides a scaffold that should provide more targeted sequencing opportunities for trait association studies using samples in the Finnish National Biobank that houses DNA from 200 000 Finns from many cohorts, including the Northern Finnish Birth Cohorts, representing about 4% of the population.
Obesity develops due to energy intake chronically exceeding energy expenditure. Higher fat content in our diet may contribute to this imbalance, as fat compared with other macronutrients is of higher energy density and efficiency. Dietary intake of fat is determined not only by its availability (and related economic and social factors) but also by the individual’s preference for fat. Fat intake is a complex behavior regulated by: (1) homeostatic mechanisms involving brain regions, such as the hypothalamus and brain stem, which serve to maintain energy balance; and (2) reward-related mechanisms involving brain regions, such as the amygdala, nucleus accumbens and orbitofrontal cortex, which process the hedonic properties of food independently of the body’s energy status. Our recent findings in the Saguenay Youth Study, a population-based study of 1,000 Canadian adolescents, suggest that reward-related mechanisms may be at play with regards to the higher risk for obesity in the context of prenatal exposure to maternal cigarette smoking (PemCS). We showed that PEMCS is associated with (1) substantial increases in body adiposity, and (2) higher preference for fat and lower volume of the amygdala. In a genome-wide association study, we also showed that (3) dietary preference for fat (as well as body adiposity and amygdala volume) is associated with genetic variation in the opioid receptor mu 1 gene (OPRM1). Finally, we have demonstrated that (4) PEMCS is associated with modifications of DNA methylation that persist into adolescence of the exposed offspring, and that (5) some of these modifications are present in OPRM1, and may inhibit expression of the protective (fat intake-lowering) allele of this gene. Taken together, our adolescent studies suggest (a) the relationships between the amygdala, dietary preference for fat and obesity; (b) perturbations of these relationships by prenatal exposure to cigarette smoke and genetic variations in OPRM1; and (c) DNA methylation as a possible molecular mechanism underlying interactions between environment (PEMCS) and genes (OPRM1).
Pain-related symptoms of temporomandibular disorders in the offspring of antenatally depressed mothers and depressed parents - a 31-year follow-up of the Northern Finland Birth Cohort 1966

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INTRODUCTION

Temporomandibular disorders (TMD) are clinical problems involving the masticatory muscles, temporomandibular joints (TMJs) and associated structures. Aspects of the aetiology of TMD are controversial. Many studies have identified an association between depression and TMD. Comorbidity of depression with other pain symptoms has also been highlighted. The aim of the study was to evaluate the association between both maternal antenatal depression and parental depression during the offspring’s childhood with symptoms of TMD in the offspring during adulthood, and to evaluate the effect of the offspring’s own depression on this association.

METHODS

In the Northern Finland Birth Cohort 1966 (n=5,541) the mothers of 12,058 cohort members were asked at mid-gestation at the antenatal clinic, whether they felt depressed. The Finnish Hospital Discharge Register (FHDR) was used to identify depression in the parents between the years 1972-1984, corresponding to offspring aged between 6 and 18 years. TMD symptoms in the offspring were detected using a computer-aided inquiry at the 31-year field study.

RESULTS

There were no statistically significant associations between TMD symptoms and maternal antenatal depressed mood. However, parental depression during the offspring’s childhood associated significantly with facial pain (adjusted OR=1.64; 1.05-2.56) and with TMJ pain at jaw rest (OR=1.81; 1.13-2.89), even after adjusting for gender, occupation of the father, family type at birth and the offspring’s self-reported depression in adulthood.

CONCLUSIONS

It can be concluded that parental depression during an offspring’s childhood increases the risk of pain-related TMD symptoms in their early adulthood.

REFERENCES

Utilizing information during the pre- and perinatal period to improve identification of developmental delay in infancy

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INTRODUCTION

Research studies examining the role of pre- and perinatal factors in infant developmental delay are limited. Addressing this gap in the scientific literature is essential in order to be able to enrich the developmental surveillance process with risk assessments performed as soon as the infant is born. This will provide an opportunity for the earliest possible identification and treatment of developmental delay. The aim of this study is to address important gaps in the scientific knowledge of infant developmental delay through:
(I) furthering the limited understanding of the factors which influence it, and
(II) evaluating the potential of utilising available information during the pre- and perinatal period to improve identification of infant developmental delay.

METHODS

The study used data from the 1966 Northern Finland Birth Cohort (NFBC1966), a prospective mother-child birth cohort (n=12,231 children). Infant developmental delay was assessed through measures of motor and language delay. Findings were validated in a second, UK-based, longitudinal birth cohort - the Millennium Cohort Study (MCS).

RESULTS

Objective I: Of the 27 pre- and perinatal factors evaluated in the NFBC1966, 6 were found to be independently and significantly associated with infant motor delay, 3 with infant language delay in boys, and 5 with infant language delay in girls. All but one of the identified factors were associated with infant motor and communicative delay in the MCS. Together, the identified factors explained only a small percentage of the variance in delayed development in the NFBC1966 (from 1.9% to 3.5%) and a larger percentage in the MCS (2.8% to 14.4%).

Objective II: The higher an infant scored on the “risk factor scale”, an additive score of the number of risk factors present for each infant, the higher the odds of being delayed in the corresponding developmental domain. In both cohorts, the percentage of delay in the highest “risk score” groups was very high, with close to half the population of infants being developmentally delayed.

CONCLUSIONS

Obtaining information on the combined presence of only a limited number of pre- and perinatal risk factors, may facilitate the identification of a large proportion of newborns which will subsequently suffer from infant developmental delay.
Menstrual disorders in adolescence: a marker for hyperandrogenaemia and increased metabolic risks in later life?


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INTRODUCTION

Hyperandrogenism per se has been suggested to be a significant metabolic risk factor in women and a cause of physical and psychological morbidity in adolescent girls. Hyperandrogenism and insulin resistance are also key features of polycystic ovary syndrome (PCOS), and women with PCOS are consequently at an increased risk of developing type 2 diabetes mellitus (T2DM) and/or metabolic syndrome. The aim of this study was to investigate whether self-reported menstrual disorders were associated with hyperandrogenaemia and metabolic disturbances already in adolescence.

METHODS

Cross-sectional study using postal questionnaires targeting 15-16-year-old girls in the Northern Finland Birth Cohort 1986 (n = 4567). 3669 girls answered the postal questionnaire and 2448 were included in the analyses. According to the questionnaire subjects were defined symptomatic (period > 35 days more than twice a year) and non-symptomatic (period < 35 days) as regards menstrual cycle.

In this study, we used the most modern and accurate methods (liquid chromatography and tandem mass spectrometry) to determine serum testosterone concentrations.

RESULTS

709 (29%) girls reported menstrual disorders (symptomatic girls) and 1739 had regular periods (non-symptomatic girls). In the whole population and both study groups, there were significant correlations between BMI (and WHR), hyperandrogenaemia and metabolic parameters. Symptomatic girls exhibited significantly higher serum testosterone (P = 0.010), lower sex hormone-binding globulin (P = 0.042) and higher free androgen indices (P = 0.002).

The two groups had comparable body mass index (BMI) and insulin sensitivity, and serum glucose, insulin and lipids. There was a significant linear trend towards higher FAI values in the higher BMI quartiles in both symptomatic and non-symptomatic girls. In the whole population there was a statistically significant linear decrease in high-density lipoprotein concentrations (P < 0.001) and higher triglyceride concentrations (P=0.004) in the upper FAI quartile.

CONCLUSIONS

Menstrual disorders at the age 16 are a good marker of hyperandrogenaemia. Our findings confirm that the association between menstrual disorders, hyperandrogenism, obesity and metabolic risks is already evident in adolescence, which strengthens the importance of recording menstrual disorders at an early stage.

REFERENCES

Functional mapping of dynamic happy and fearful facial expressions in young adults with familiar risk for psychosis


INTRODUCTION

Social interaction requires mirroring to other people’s mental state (1). Psychotic disorders have been connected to social interaction and emotion recognition impairment. We compared the brain activity between young adults with familial risk for psychosis (FR) and controls during visual exposure to emotional facial expression.

METHODS

51 FR and 51 control subjects were drawn from the Northern Finland 1986 Birth Cohort (Oulu Brain and Mind Study). None of the included participants had developed psychosis. The FR group was defined as having a parent with psychotic disorder according to the Finnish Hospital Discharge Register.

Participants underwent fMRI imaging using visual presentation of dynamic happy and fearful facial expressions. FMRI data were processed to produce maps of activation for happy and fearful facial expression, which were then compared between groups.

RESULTS

FR subjects had increased activity in premotor cortex and reduced deactivation of prefrontal cortex (PFC) structures during happy facial expression. There were no between-group differences during fearful facial expression. The between group differences are presented in figure 1.
CONCLUSIONS

Increased activations by positive valence in FR were in brain regions crucial to emotion recognition and social interaction (2). Our study had two main results. Increased activation of premotor cortex may serve as a compensatory mechanism as FR subjects may have to exert more effort, as has been found earlier in schizophrenia (3). Secondly we discovered that FR subjects fail to deactivate PFC structures which may imply error in Default mode network (4). The latter finding has not been discovered in previous FR studies with facial stimuli.

REFERENCES


SNPs for dopamine receptor D2 predict adverse neurocognitive outcomes in young people at high risk for psychosis but not population controls in the Northern Finland Birth Cohort 1986

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INTRODUCTION

Neurocognitive intermediate phenotypes for psychosis have been increasingly demonstrated in those at high risk for psychosis¹,². Candidate genes for neurocognitive performance in psychosis include the dopamine receptor D2 (DRD2) gene, which has been associated with schizophrenia³ and adverse cognitive outcomes in schizophrenia⁴. However, there is limited research linking these associations to candidate genes in populations at risk for psychosis. We explored the association between two established psychosis risk variants in DRD2 (rs1800497 and rs6277) and neurocognitive performance in individuals at risk for psychosis (either familial or clinical risk), who were recruited from a population birth cohort.

METHODS

The subjects of this study were members of a subsample of the Northern Finland Birth Cohort 1986 (NFBC 1986). Subsamples at elevated familial risk (n=61) or clinical risk (n=45) were recruited for the Oulu Brain and Mind Study. Clinical risk for psychosis was confirmed using the Structured Interview for Prodromal Syndromes (SIPS). These were compared with a population control group recruited from the NFBC 1986 (n=74).

Neurocognitive performance was evaluated using a comprehensive battery of neurocognitive tests, which were condensed for analysis using exploratory factor analysis.

The association between these neurocognitive factors and two SNPs (rs1800497 and rs6277) were then measured using linear regression, controlling for gender, education and type of risk in the risk group.

RESULTS

Exploratory factor analysis supported a three-factor model for neurocognitive performance, with predominantly verbal, psychomotor and non-verbal factors.

The SNPs were not directly associated with clinical or familial risk for psychosis. They were also not associated with neurocognitive performance in the control group. However, the minor allele of rs1800497 was strongly associated with poorer
psychomotor performance (Cohen’s $f^2=0.47$, $P=0.002$) and the minor allele of rs6277 was strongly associated with poorer verbal performance (Cohen’s $f^2=-0.51$, $P=0.001$) in the combined risk group.

**CONCLUSIONS**

These results suggest that two well-characterized SNPs at DRD2 are associated with adverse neurocognitive outcomes in those at risk for psychosis but not a control population. The finding in relation to rs6277 is consistent with previous findings regarding sustained attention in a Chinese sample with schizophrenia\(^4\). It is interesting that these associations were not found in the control population group, suggesting that further risk element is necessary for this neurocognitive outcome. Both SNP findings in the risk group require replication and larger samples that would allow comparison of those with familial risk to those with clinical risk.

**REFERENCES**


Brain structural deficits and working memory dysfunction in adults who were diagnosed with ADHD in adolescence

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INTRODUCTION

We compared brain structure and working memory function in young adults that were diagnosed with ADHD in adolescence and a matched control group. We tested the hypothesis that subjects diagnosed with ADHD during adolescence present residual brain abnormalities both in brain structure and in working memory function.

METHODS

83 young adults (aged 20-24 years) from the Northern Finland 1986 Birth Cohort were classified as diagnosed with ADHD in adolescence (adolescence-ADHD, n=49) or a control group (n=34). T1-weighted brain scans were acquired and processed in a voxel-based analysis using permutation-based statistics. A sub-sample of both groups (ADHD, n=21; Controls n=23) also performed a Sternberg working memory task whilst acquiring fMRI data. Areas of structural difference were used as a region of interest to evaluate the implications that structural abnormalities found in the ADHD group might have on working memory function.

RESULTS

There was lower grey matter volume (GMV) bilaterally in adolescence-ADHD participants in the caudate (p<0.05 FWE-corrected across the whole brain) at age 20-24. Working memory was poorer in adolescence-ADHD participants, with associated failure to show normal load dependent caudate activation.
CONCLUSIONS

Young adults diagnosed with ADHD in adolescence have structural and functional deficits in the caudate associated with abnormal working memory function. These findings are not secondary to stimulant treatment as only one patient received medication for ADHD, and emphasize the importance of taking a wider perspective on ADHD outcomes than simply whether or not a particular patient meets diagnostic criteria at any given point in time.
Experiences of loneliness from childhood to adulthood. Northern Finland Birth Cohort 1986 study

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INTRODUCTION

The aim of this PhD study is to examine how loneliness manifests itself over the life-time of young people in Northern Finland and to look what consequences it has for their well-being, health and growth. Humans are social beings and when one’s socioemotional needs are not adequately met, the involuntary, subjective, negative feeling of loneliness may occur\textsuperscript{1}. Loneliness has been associated with many negative outcomes such as depression, bullying, eating and sleeping disturbances and suicidal behaviour. Left unattended, loneliness may have serious consequences on one’s mental and physical well-being and health\textsuperscript{2}.

METHODS

The synopsis of the dissertation is composed of four articles. Study is a mixed method work; in articles 1-3 multinomial logistic and logistic regression were used to address associations of loneliness with selected variables in Northern Finland Birth Cohort 1986 data (NFBC 1986). In the fourth article 39 semi-structured interviews of those members of cohort data who stated to be very lonely at age 16, were conducted. Interviews were analyzed using qualitative, deductive, unconstrained content analysis\textsuperscript{3} to address the lived experience of loneliness.

RESULTS

First article\textsuperscript{4} examined how selected social, emotional and certain factors of health and well-being were associated with 16-year-olds loneliness experiences (n=7,014). In total, 3.2% (girls: n=149, 4.1%; boys: =73, 2.2%) reported feeling very lonely, 26.4% (girls: n=1267, 34.8%; boys: n=586, 17.4%) reported to be somewhat lonely and 70.4% (girls: n= 2225, 61.6%; boys: n=2714, 80.5%) were not lonely. Multinomial logistic regression showed that factors associated with being very lonely in comparison to not being lonely were: not having close friends (girls odds ratio (OR) 15.1; boys OR 4.4), feeling unliked (girls OR 6.5; boys OR 6.3) being bullied (girls OR 4.2; boys OR 3.6), feeling unhappy, sad or depressed (girls OR 6.5; boys OR 5.3), being dissatisfied with life (girls OR 3.0; boys OR 2.2), and having poor self-rated health (girls OR 2.5).
In the second article it was examined whether associations exist between deliberate self-harm (DSH) or its ideation and loneliness among 16-year-olds. 8.7% (n=608) of adolescents reported DSH often/sometimes with girls (n=488, 13.4%) reporting DSH almost 4 times than that of boys (n=120, 3.6%). Logistic regression showed that those who reported to be very lonely (girls OR 4.1; boys OR 3.2) and somewhat lonely (girls OR 2.4; boys OR 2.4) were more likely to report DSH than those without these feelings.

In the third article it was examined how loneliness and social relations, self-esteem, academic achievement and demographics are associated with school liking. Multinomial logistic showed that not liking school at all in comparison to neutral attitude was associated among girls with being very lonely (OR 2.9), among boys not having close friends (OR 2.0) doing poorly at Finnish language (OR 2.6) and for both spending time with adolescents who get a lot in trouble (girls OR 5.8; boys: OR 5.8).

Preliminary results of the final article shows that among interviewees (n=39, aged 27-28), 24 (61%) had moved out from Northern Finland, 35 (90%) have been bullied, 21 (54%) have had some sort of mental issues (depression, Asperger, ADD), and 8 (21%) had suicidal behavior (DSH, suicidal attempt or ideation). Still most of them had at least one close friend and only 8 were single and living alone. Loneliness was portrayed as a negative and painful experience. The results from first three articles were largely confirmed in the interviews.

**CONCLUSIONS**

Loneliness should be considered as a risk for individual health and wellbeing. It is important to recognize lonely individuals early on to prevent more serious problems which loneliness is associated. Special attention should be paid on school, which can be difficult environment to many; loneliness, bullying, exclusion and non-belonging might cause serious long term negative effects later on. Enhancing non-violence, belonging, compassion and empathy in schools is important.

**REFERENCES**

Lifecourse programming of obesity and type 2 diabetes

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INTRODUCTION

A large body of evidence is describing the life-course programming of the risk of obesity and type 2 diabetes. The focus of our research aims to study the pathways predisposing the risk of obesity and type 2 diabetes. We are focusing on full translationality for clinical relevance in humans taking into account the lifecourse interplay between lifestyle, environmental and genetic factors.

The objective of the projects we are undertaking aims in particular to characterize 1) the time dependent epigenetic processes and 2) the gene-environment-time interactions induced by the exposure to adverse metabolic environment in early life. This includes the exposure to adverse pregnancy outcomes:
- Fetal growth restriction
- Gestational obesity
- Gestational diabetes
- Maternal and familial stressors

The project further studies the interaction with early postnatal growth understanding in part the postnatal process in the acquisition of mature and functional adiposity.

METHODS

The research methods we are developing together with epidemiologists, statisticians, biochemists and molecular biologist explore the time-dependency for gene-environment interactions and the lifecourse paths affecting the epigenetic programming of adiposity and impaired glucose tolerance. My current research combines analysis in the Northern Finland Birth Cohorts together with functional studies in transgenic animals and physiological models.

The methods we are developing include:
- Genome-wide meta-analysis
- Gene-environment interactions
- Epigenetics and epigenomic wide-association study
- Brain and body imaging

\textbf{Figure 1.} The sensitive windows of programming
RESULTS AND CONCLUSIONS

Optimal health in early life is critical to lay the foundations for healthy and active ageing for future generations. This can reduce the burden of childhood obesity and subsequent life-long impairment throughout adult life. We will use discoveries generated in young populations to help promote lifelong good metabolic and psychosocial health. The research is expected to identify novel molecular and phenotypic pathways, which can be used to improve the early detection of pre-diabetic states, develop tailored medicine strategies, and protect cognitive and psychosocial functioning. In addition, improving the health of the young population in Europe, to enable healthy and active ageing, will have significant future benefits and cost-savings.
Understanding the bi-directional relationship between impaired glucose tolerance and employment related adversities

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INTRODUCTION

A large body of evidence is describing a spiralling relationship between social inequities and impaired glucose homeostasis¹. In order to understand the social processes that stratify health outcomes in adulthood, the conditions of working life have to be also considered². Studies have shown for example that shift work, rotating night shift work and working overtime³ are risk factors for type 2 diabetes. In fact, while adversities⁴ during the working life may causally associate with the incidence of T2D, the reciprocal association is also observed.

The present project is exploring the relationship between the differing employment paths upon impaired glucose tolerance on the one hand, and on impaired glucose tolerance on employment paths on the other hand, with a special reference to unemployment. We aim to explore the role played by the sex and the gender in modulating the relationship.

METHODS

Our present on-going project is studying the bi-directional effects of working life adversities to glucose metabolism - and glucose metabolism to working-life adversities and proposes to look at the mediation through stress. The project combines the research on the NFBC 1966 cohort at 31 to 46 y targeting the period of the life course where both the working life and the metabolic health determinants are undergoing major changes. The second part of the project uses the data from the FinD2D program in a population characterised by prediabetic states.
RESULTS AND CONCLUSIONS

The present proposal is aiming to describe the bio and social relationship between the employment paths and T2D. Our own research and data collected from other research cohorts (e.g. Whitehall II, GAZEL) establishes a possible specific elicitation of the risk for T2D by the adversities of working life. Both the impact of i) unfavourable paths in the working-life on T2D and ii) of T2D on the employment paths represent health and societal priorities and will be tested in the present project. Understanding the bio-social characteristics of complex diseases such as T2D is currently considered a priority in Europe in order to preserve the health and social system 3. Our research is expected to be original and to advance the research in the etiology, pathophysiology and the consequences of impaired glucose metabolism and T2D.

We finally aim to implement our research into the clinical practice. We hypothesize that a holistic approach, including routine detection of the most important measures of the social adversities leading to stress, would improve both diagnostic accuracy and the adequacy in choosing the most suitable treatment options for impaired glucose metabolism in the health care practice. By this readily available personalized approach, the accuracy and effectiveness of treatment would help in sustainable promoting of public health and social functioning. Importantly, a thoughtful considering of also gender and sex in choosing between treatment alternatives for impaired metabolism would add to the prevailing routines. In practical terms, the findings of this study can be implemented in the structured models of the medical records using ICT solutions and as potential outcomes to be followed in evaluating the effectiveness of care.

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Indicators and risk factors for periodontitis and dental caries

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BACKGROUND

In Finland, oral health status has improved among adult population in the past 20 years, but the oral health related problems are still common. In the national Health 2000 survey, 64% the Finnish adult population aged 30 years or more had at least one tooth with deepened periodontal pocket (PD ≥ 4 mm, and severe forms of periodontitis (PD ≥ 6 mm) were found in 21% of the population (1). According to the Health 2000-survey every third adult had dental caries. Women had less dental caries and reported brushing their teeth significantly more frequently than men (1).

Previous research has shown male gender, poor oral hygiene, poor oral health behavior, low education level, smoking and other health related behaviors to be related to periodontal diseases and dental caries (1, 2). In addition, host immune responses play an important role in the initiation and progression of periodontitis (3, 4) and recent studies have shown associations between periodontitis and several systemic conditions, such as diabetes mellitus (5), cardiovascular diseases (6, 7), and obesity (8, 9).

The World Health Organization (WHO) recommends use of DMF criteria for caries detection in epidemiological studies (number of Decayed (D), Missing (M), and Filled Teeth (F)) (10). A new method has been developed to improve reliability of dental caries diagnostics, ICDAS (International Caries Detection and Assessment System).

AIMS

The general aim is to characterize risk factors for periodontal infection and to identify risk groups for gingivitis and periodontitis for early preventive care. Another aim is to identify risk groups for dental caries.

In the first stage, our aim is to develop a periodontal indicator (outcome variable) using the site based periodontal data collected in the clinical periodontal and radiographic examinations.

Regarding dental caries our aim is to find best combinations of caries indicators based on ICDAS scores (1-6) for initial and manifested dental caries lesions and categorize individuals accordingly to those with no or little caries activity and those with high activity.

For further research, our aim is to assess associations between health behavior and related background variables (gender, education, smoking, etc.), and periodontal disease/dental caries by utilizing selected indicators.

METHODS

Data: The NFBC 1966 study population.

Outcome variables: developed indicators of periodontal infection; developed indicators of dental caries
based on the F index, ICDAS score and presence of periapical parodontitis.

Explanatory variables: general health data and associated medications.

Dental health associated background variables: gender, socioeconomic factors, smoking, dental health behavior, use of services, perceived dental health.

**PROGRESS**

Initial descriptive analyses have been done to obtain a general view of the distribution of main study variables.

**RESEARCH GROUP**

Professor Jorma Virtanen (the main investigator), MSc Toni Similä, Department of Community Dentistry, Professor Pekka Ylöstalo and Professor Tellervo Tervonen, Department of Periodontology and Geriatric Dentistry, Associate Professor Vuokko Anttonen and Associate Professor Marja-Liisa Laitala, Department of Cariology, Endodontology and Paedodontics, MSc Paula Pesonen.

**REFERENCES**


Bone fractures – a comprehensive birth-cohort research of their epidemiology, genetics, predisposing risk factors and long-term outcomes in northern Finland

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BACKGROUND
Fractures are usually being responsible for most morbidity in childhood. Before the age of 16 years half of boys and a third of girls have suffered from a bone fracture¹. Thereafter, the annual risk of fractures holds stable (or decrease in males) until the age of about 50–60 years, when a new increase initiates². The overall fracture incidence of normal urban population is about 10–20 per 1000 people every year³. Regardless the importance of fractures as a general health problem and economic burden, there are few reports of annual fracture incidence in both children and adults and the epidemiology of fractures is still not well known⁴.

Many factors affect individual’s susceptibility to fractures: it is not understood why some will suffer from a bone fracture while other will not. Despite the accumulation of all injuries in some socio-economic groups, the association between the low socio-economic status (SES) and increased fracture risk is sparse or controversial⁵. Instead, genetics, several chronic diseases, way of life of both the parents and the patients themselves and multiple external contributors (e.g. vitamin substitutions) have been associated with bone health and the risk of bone fractures⁶,⁷.

DESCRIPTION OF THE STUDY
In this large Oulu Fracture Study we aim to analyze the epidemiology of fractures. We aim to determine overall (annual) incidence of hospital-treated fractures and fracture pattern according to increasing age. Further, the association of SES with fractures is aimed to be determined. We also aim to study predisposing risk factors of the fractures as well as their genetic background. The short-term and long-term outcomes of the fractures are to be analyzed, focusing on the association between preceding fractures and osteoarthritis (OA) in adulthood.

A prospective birth-cohort (1966) study (N=12.058) in two northernmost provinces of Finland was performed (NFBC 1966). Data were collected in prenatal clinics and at birth by questionnaires and clinical evaluations. Thereafter the cohort members have been followed by study investigation visits and postal questionnaires until the age of 46 years (at 2013). Another part of the study data includes 9,432 live-born members in 1986 (NFBC 1986). The cohort has been
surveyed during gestation, at birth, at the ages of 7-8 years and 15-16 years in means of postal questionnaires and clinical tests, including bone density measurements in a given subgroup. All members of both cohort populations will be followed up as regards with their fractures. Information of the fractures from birth to 46-years or 28-years of age, respectively, is obtained from the Finnish Hospital Discharge Register (FHDR). Furthermore, as regards with the sub-populations of the cohort members living within the area of Oulu University Hospital, the internal institutional registries of the fractures will be used. The epidemiology of fractures will be described in detail. According to the aim, not only the overall fracture incidence but also the yearly incidence of the fractures at specific anatomic sites will be evaluated. The cranium, spine, upper and lower extremities, thorax and pelvis will be investigated separately for both sexes. A risk of a new consecutive bone fracture following the previous bone fracture will be studied. Fractures caused by sports injuries are to be separately analyzed. The preceding factors of fractures will be analyzed, focusing on gestational or postnatal observations (weight gaining, delayed growth), maternal smoking, obesity and way of life, bone density and factors related to bone density (physical activity) and eating habits (e.g. calcium and D-vitamin intake). In addition, the genetic background of the bone health disturbances and fractures will be investigated. The role of preceding fractures in weight-bearing bones in following OA or other degenerative disorders will be surveyed.

PRELIMINARY FINDINGS

There are few results available. According to the preliminary epidemiological analysis the total life-time incidence of hospital-treated fractures until the age of 46-years was 135.6 per 1000 in the NFBC-1966 population. During the first 18 years of age there were two peaks in the fracture occurrence: the first peak was at 7 years of age and another in the late adolescence. The upper extremity fractures were more common in younger children and lower extremity fractures in adolescents (Fig. 1).

Figure 1. The fractures in the upper extremity (line) were most common at the age of 7 years. Lower extremity fractures (dot-line) were most usual at 16-years of age. N / 1000 cohort members.

SUMMARY

Fractures cause acute decrease in health and well-being. Later, they can result in long-term chronic morbidity such as OA. Using our unique cohort studies, we are going to perform a comprehensive analysis of the epidemiology of bone fractures. We will also study the genetic background, risk factors and long-term outcome of children’s and adults fractures.

REFERENCES

High prevalence of skin diseases and need of treatment in a middle-aged population - A Northern Finland Birth Cohort 1966 study

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INTRODUCTION

Skin diseases are common and they load health care resources\textsuperscript{1}. About one in every three of all patients at general practitioner suffers from a skin disorder\textsuperscript{2,3}. Most dermatologic diseases are chronic in nature and decrease the daily quality of life\textsuperscript{4}. Nevertheless, the epidemiological studies addressing overall prevalence of skin diseases at population level are sparse\textsuperscript{1,5,6,7} and two noteworthy studies among these were conducted as early as in the 1970s\textsuperscript{1,5}.

Due to the scarce epidemiological-level evidence of the prevalences of skin diseases we decided to study the overall prevalence of all skin disorders among an unselected middle-aged population in a developed country. Another aim was to investigate the possible sex differences in skin diseases and finally, the association between skin diseases and socioeconomic status.

METHODS

To find out the overall prevalence of skin diseases a whole body skin examination was performed by a specialist in dermatology or an experienced resident for 1932 study cases (46 years of age). All reached study cases (60.7\% of 3181) were living in a given geographical area; in the city of Oulu or 100 km of it. These cases belong to Northern Finland Birth Cohort 1966 (NFBC 1966) that is a comprehensive longitudinal research program (N=12 058). In order to analyze the association between education level and skin diseases, the study cases were classified for three subgroups of education. This background information was obtained from National Education Register and from self-reported questionnaires. According to found skin finding or disease it was decided for every study case whether any follow-up or treatment were required.

RESULTS

A high prevalence of all skin diseases needing treatment was found (N=1158, 60\%). Half of the cases of skin findings were evaluated to be serious enough to require diagnostic evaluation, treatment or follow-up either in a general health care, occupational health care or a secondary care setting. The remaining half were thought to be slight and self-treatment was advised. Males (70\%) had more skin diseases needing treatment than females (52\%) (P<0.001). The most
common skin finding was a benign skin tumor, which was found in every cohort member. Skin infections (44%), eczemas (27%) and sebaceous gland diseases (27%) were the most common skin diseases in the cohort. Moreover, skin infections and eczemas were more commonly seen in the group with low education compared to those with high education (P<0.005).

CONCLUSIONS

The results strengthen the postulate that skin diseases are common in an adult population. In clinical practice it means that careful skin evaluation is an important and essential part of medical examination which presents a challenge to general practitioners and other physicians. We also found that low socioeconomic status and sex have an influence on the prevalence of skin diseases.

REFERENCES


Association between childhood specific learning difficulties and school performance in adolescents with and without ADHD symptoms: a 16-year follow-up

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INTRODUCTION
Approximately 5% of all public school children are identified as having special learning difficulties (SLDs)1, but higher figures have been presented. In a follow-up study from Australia, 36.6% of the primary and secondary school children were identified as having some area of special learning needs in their first school year2. A large survey of the lifetime prevalence of learning disabilities and special health care needs of children under 18 years in the U.S. indicated the prevalence to be 9.7% and, depending on the number of definitional criteria the prevalence of learning disabilities ranged from 15.0 to 87.8%3. In Finland, 21.2% of school-aged children were referred to special education because of learning disabilities in the year 2001 and 28% were referred in the year 20044. Previous research provides strong support for the connection between learning disabilities and Attention Deficit Hyperactivity Disorder (ADHD)5. The studies by Mayes et al.6 indicated that as many as 70% of the children with ADHD have comorbid learning problems. Despite broad research on this area, few studies utilized epidemiological samples or longitudinal design. Our earlier study7 from the Northern Finland Birth Cohort 1986 (NFBC 1986) indicated that at the age of 8, the cross-sectional association between learning difficulties and behavioural problems was clear. Now we examined whether this association still exists when the children are 15/16 years old and, if so, in what way it associates with the school performance and future educational plans. The specific aim was to investigate whether childhood SLDs predict later poor school performance (assessed as school grades and their mean values, grade repetition) of adolescents with and without ADHD symptoms, and how SLDs affect their educational aspirations.

METHODS
Our sample is based on an unselected, general population from the Northern Finland Birth Cohort 1986. The original study population consists of 9432 live born children, born between July 1st 1985 and June 30th 1986 in the two northernmost provinces of Finland. At the time of the first follow-up, when the children were 7 and 8 years old8. The second follow-up was conducted, when the adolescents were 15/16 years old. Data were collected using questionnaires for parents and teachers at ages 7 and 8, and for parents and adolescents at ages 15/16. Information on adolescents’ school performance in the final year of
comprehensive school was obtained from the national application register.

**RESULTS**

In the study population the occurrence of SLDs at 8 years was 19.9% (n=1198) and ADHD symptoms at 15/16 years was 8.0% (n=530). Among boys, the occurrence of SLDs was 24.5% (n=734) and among girls was 15.3% (n=464, p <0.0001) at 8 year. ADHD symptoms were more common among boys at 10.4% (n=346) than girls at 5.6% (n=184, p <0.0001) at 15/16 years. Comorbid ADHDs and SLDs existed in 3.0% of the study population (n=179). Among boys the comorbidity was 4.5% (n=136) and among girls was 1.4% (n=43, p <0.0001) at 15/16 years. Most of the adolescents attended comprehensive school. However, among the adolescents with comorbid ADHDs and SLDs as much as 18.3% reported to attend vocational and 8.5% special school compared to the group without problems where the figures were 7.2% for vocational and 0.3% for special school. Twelve percent of boys and 11% of girls with comorbid ADHDs and SLDs had repeated a grade. The difference was statistically significant compared to other groups. Results of the linear regression analysis for school performance of the boys and girls indicated that having ADHD symptoms but not learning difficulties or having both was associated with a statistically significantly lower mean value of school grades for the theoretical subjects. For girls, comorbid ADHDs and SLDs seemed to cause great difficulties in Finnish (OR 10.40, 95% CI 4.81-22.51) and in mathematics (OR 9.24, 95% CI 4.48-19.07). Our findings indicated that the association of poor school performance was stronger with ADHD symptoms than with learning difficulties, although it is worth noting that the confidence intervals of the estimates overlapped. The adolescents were also asked about their plans for future education. The adolescents with comorbid ADHDs and SLDs were planning to aim for a vocational qualification (46.5%) more often than those in other groups. Conversely, the adolescents without problems planned to go to polytechnic, college or university (44.4%) more often than adolescents with problems (5.8%).

**CONCLUSIONS**

We conclude that ADHDs and SLDs may have significant effects on adolescents’ school performance and their educational plans for the future. Comorbid ADHDs and SLDs, particularly, have a strong negative influence on school performance. Thus these problems should be recognized and diagnosed as early as possible. Special support should be given to children with ADHDs and/or SLDs, because working under a normal schedule can be frustrating to these children. Even though the background of a child’s learning difficulties or

**REFERENCES**

Physical activity and fitness during the life course

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INTRODUCTION

This presentation summarizes the findings on the early life determinants of physical activity and fitness in adolescence and adulthood from the Northern Finland Birth Cohort 1966 and 1986 studies (NFBC).

The future directions of NFBC studies in the area of physical activity, fitness and health will also be discussed.

METHODS

In the NFBC 1986 study, physical activity and time spent in sedentary behaviour were self-reported, and cardiorespiratory fitness was measured by submaximal cycle ergometer tests at age 16 (in 2002).1,2

The NFBC 1966 study included self-reported physical activity at the ages of 14 and 31, in 1980 and 1997 respectively.3-6 At year 31, physical fitness was measured by step test, and muscular fitness was measured by hand grip and isometric trunk extension tests.7,8

In the 2012–2014 data collection, when the participants were 46 years old, physical activity was also measured objectively by accelerometers.

RESULTS

Birth weight, infant weight gain and the milestones of motor development were related to later physical activity and physical fitness.

Andersen et al.9 conducted a meta-analyses (including the NFBC studies) to investigate the correlations between birth weight and leisure-time physical activity in adolescence and adulthood. The association between birth weight and physical activity was weak within the normal birth weight range, but both low and high birth weights were associated with physical inactivity, which may be a mediator between prenatal influences and later disease risk9 with higher grade in school physical education at 14 years. In addition, the age at walking while supported was positively associated with the number of different sports reported and a greater frequency of sports participation at age 14.10 Children with suspected motor problems and low preference for physically active play at 8 years tended to have a higher risk of being physically inactive at 16 years.11 In addition, higher birth weight, lower infant weight gain and earlier infant motor development predicted higher levels of muscular and aerobic fitness at 31 years.12

Physical activity in youth was positively associated with physical activity in adulthood. Frequent participation in sports after school, being a member in a sports club and high grade in school physical education at 14 years were associated with a high level of physical activity at 31 years.4,5 The effect of participation in different types of sports in youth was also evaluated. Adolescent participation in rather intensive endurance sports and sports that required or encouraged diversified sports skills appeared to be the most beneficial with respect to adult physical activity.4
CONCLUSIONS

To promote physical activity and fitness successfully among young people and adults, it is essential to understand the factors that can either limit or facilitate physical activity at different phases of the life course from childhood through adulthood.

REFERENCES

Key references are related to physical activity and fitness measurements used in the NFBC studies and the key findings described in the abstract.

Perinatal factors associated with physical activity and cardiorespiratory fitness in adolescence

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INTRODUCTION
Adolescents and adults born at high and low ends of the birth weight distribution undertake less leisure-time physical activity than those born at average birth weight (1) and those born at low birth weight have lower physical performance (2). The role of factors underlying birth weight has been less investigated. First, we tested whether the previously found relationship between birth weight and low levels of physical activity is also observed in the association between birth weight and cardiorespiratory fitness. Second, we studied whether birth weight associated perinatal factors, such as gestational age, maternal BMI, maternal hypertension and risk factors for gestational diabetes contribute to these associations.

METHODS
Of the 16-year-old members of the population-based Northern Finland Birth Cohort 1986, 6682 singletons with no major physical disability reported the amount of light, brisk and commuting physical activity outside school hours and 4706 completed a submaximal cycle ergometer test for the assessment of cardiorespiratory fitness. Physical activity was summarized as metabolic equivalent hours (METhours) per week and peak oxygen uptake relative to body weight (ml/kg/min) calculated by heart rate responses. To assess the effect of perinatal factors on the outcomes, the adequate data were analyzed by multiple linear regression.

RESULTS
A one kg higher birth weight was associated with 0.62 METh/week (95% CI -0.16 to 1.41 adjusted for sex) lower level of physical activity and 0.80 ml/kg/min (0.34 to 1.27) lower peak oxygen uptake. Similar associations were observed with birth weight SD score as a predictor. Association between gestational age and physical activity was inverse U-shaped such that adolescents born at both ends of the range of gestational age undertook less physical activity than others. These adolescents also seemed to
Table 1. Perinatal factors, physical activity and cardiorespiratory fitness in adolescence

<table>
<thead>
<tr>
<th>Perinatal exposure</th>
<th>Self-reported physical activity (METh per week)</th>
<th>Cardiorespiratory fitness, peak oxygen uptake (ml/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean difference (95% CI)</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>0.19 (-0.45;0.08) †</td>
<td>0.18 (-0.34;0.03)</td>
</tr>
<tr>
<td>Maternal risk factors for GDM §</td>
<td>6675</td>
<td>4701</td>
</tr>
<tr>
<td>Risk factors but normal OGTT</td>
<td>-1.77 (-3.23;-0.30)</td>
<td>-0.91 (-1.75;-0.07)</td>
</tr>
<tr>
<td>GDM</td>
<td>-1.02 (-4.90;2.85)</td>
<td>-2.28 (-4.44;-0.13)</td>
</tr>
<tr>
<td>Maternal hypertension in pregnancy ll</td>
<td>-0.49 (-1.64;0.65)</td>
<td>-0.51 (-1.19;0.16)</td>
</tr>
<tr>
<td>Maternal BMI before pregnancy, kg/m²</td>
<td>-0.12 (-0.24;0.00) ‡</td>
<td>-0.24 (-0.31;-0.17) †</td>
</tr>
<tr>
<td></td>
<td>6533</td>
<td>4606</td>
</tr>
</tbody>
</table>

*The linear regression models are adjusted for sex. Mean differences (95% CI) are presented per one unit higher value or compared with control group. Quadratic trend, p value † < 0.05, ‡ 0.05.
§Control group includes adolescents not exposed to maternal risk factors for GDM or type 1 diabetes in pregnancy.
ll Maternal hypertension (gestational or chronic and preeclampsia including superimposed). Control group includes adolescents not exposed to hypertension during pregnancy.
Abbreviations: CI, confidence interval; GDM, gestational diabetes; OGTT, oral glucose tolerance test.

Adolescents whose mothers were obese (BMI > 30 kg/m²) undertook 3.43 (95% CI 1.20 to 5.65) METh per week less physical activity than those whose mothers had normal BMI. When maternal BMI was used as a continuous variable, there was a borderline inverse association between maternal pre-pregnancy BMI and physical activity and an inverse association between maternal pre-pregnancy BMI and peak oxygen uptake.

Adolescents exposed to maternal risk factors for gestational diabetes undertook less physical activity and had lower peak oxygen uptake, although the results of physical activity were not statistically significant in GDM group.

Maternal hypertension during pregnancy was not associated with either of the outcomes.

CONCLUSIONS

Our results show that the pregnancy related factors, including gestational age, maternal BMI and risk factors for gestational diabetes, underlying the association of birth weight with physical activity are also associated with lower cardiorespiratory fitness in adolescence. Maternal hypertension, however, was not associated with either of the outcomes.

REFERENCES

Physical activity and endometriosis risk

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INTRODUCTION

Life style factors seem to play a role in the development of endometriosis. There is data about physical activity and body size, but the results are not consistent. Endometriosis and low BMI have been found to be associated in many epidemiological studies. On the other hand, physical activity in adulthood has been reported to lower the risk for endometriosis. This is quite controversial, because regular exercise lowers body mass. Many of these studies are case-control designs and the results might be biased due to patient group selections. Cohort studies give more reliable data for risk-factor analysis. The aim of this study was to investigate the relation of endometriosis and physical exercise frequency in adolescence and adulthood. The association to different sports was evaluated.

METHODS

There are 215 endometriosis cases in the NFBC, giving a 3.7% prevalence. The diagnosis data was collected from the hospital discharge register. The physical activity data was collected by follow-up questionnaires carried out in 1980 and 1997-1998, at the ages of 14 and 31. The response rate was 97% at age 14 and 75% at age 31. There were questions concerning physical activity frequency and participation in different types of sports.

RESULTS

Frequent physical activity at adolescence presumes endometriosis. When categorizing activity levels in three classes: rarely (1-3 times a month or not at all), weekly and often (every day or every other day), at age 14 the prevalence of endometriosis increased from 3.8% to 4.7% to 5.4% (p<0.009). At age 31 the prevalence increased from 3.7% to 5.1% to 5.0% (NS). Women who were later diagnosed with endometriosis listed several endurance sports at age 14: running, swimming and several individual sports: downhill skiing, gymnastics, dancing

CONCLUSIONS

This analysis suggests that physical activity has a role in the development of endometriosis. Women who are physically inactive at adolescence and at adulthood seem to have a lower risk for endometriosis. There seems to be an association between very active and physically demanding sports and later diagnosis for endometriosis. Life style factors seem to have far-reaching and unexpected consequences for female health. The mechanisms remain unsolved.
INTRODUCTION

Studies show evidence of longitudinal brain volume decreases in schizophrenia. We studied brain volume changes and their relation to symptom severity, level of function, cognition, and antipsychotic medication in subjects with schizophrenia and control subjects from a general population based birth cohort sample in a relatively long follow-up period of almost a decade.

METHODS

All members of the Northern Finland Birth Cohort 1966 with any psychotic disorder and a random sample not having psychosis were invited for a MRI brain scan, and clinical and cognitive assessment during 1999-2001 at the age of 33-35 years. A follow-up was conducted 9 years later during 2008-2010. Brain scans at both time points were obtained from 33 subjects with

schizophrenia and 71 control subjects. Regression models were used to examine whether brain volume changes predicted clinical and cognitive changes over time, and whether antipsychotic medication predicted brain volume changes.

**RESULTS**

The mean annual whole brain volume reduction was 0.69% in schizophrenia, and 0.49% in controls (p=0.003, adjusted for gender, educational level, alcohol use and weight gain). The brain volume reduction in schizophrenia patients was found especially in temporal lobe and periventricular area. Symptom severity, functioning level, and decline in cognition were not associated with brain volume reduction in schizophrenia. The amount of antipsychotic medication (dose years of equivalent to 100 mg daily chlorpromazine) over the follow-up period predicted brain volume loss (p=0.003 adjusted for symptom level, alcohol use and weight gain).

**CONCLUSIONS**

In this population based sample, brain volume reduction continues in schizophrenia patients after the onset of illness, and antipsychotic medications may contribute to these reductions.
Osteoarthritis and musculoskeletal symptoms in NFBC1966: epidemiology and risk factors

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INTRODUCTION

Osteoarthritis (OA) is generally considered as a multifactorial, complex disease. It is characterized by softening and fragmentation of the protective cartilage layer of articulating joints causing serious medical, social and economic problems worldwide. OA can affect different joints and is most common in lumbar and cervical spine, specific hand joints, knees and hips. OA is usually diagnosed based on a physical exam and imaging, most often x-rays. However, radiological involvement and pain seem to have a poor correlation.

Well known risk factors for OA include age, obesity, injuries and deformities of the hip and knee. Also genetic factors have a significant role: the heritability of OA has been estimated to be 39-70%, depending on the joint examined¹. Nevertheless, the disease generally lacks a clear Mendelian pattern of inheritance. Probably all cases have both genetic and environmental background, which creates a great challenge for understanding the etiology of the disease.

Metabolic syndrome (MetS) is a common phenotype that increases the risk for cardiovascular disease. Central components of the syndrome are insulin resistance, visceral obesity, atherogenic dyslipidemia and hypertension. Family studies have suggested that 40-70% of the inter-individual variation in obesity risk and body mass index (BMI) can be attributed to genetic factors². OA and MetS share age and obesity as risk factors, and they both have been considered as an inflammatory disease. Obese patients with MetS have a higher risk of OA compared with obese patients without MetS³. People with MetS also develop OA at an earlier age and have more generalized pathology, increased inflammation, and intensive pain in the joints when compared with patients with OA without MetS⁴. The role of each component of MetS in the development of OA remains to be discovered.

OBJECTIVES

The principal aims of this research are:

1. To study the current epidemiology of osteoarthritis and musculoskeletal symptoms in the northern Finland population at the ages of 31 and 46 based on the Finnish National Hospital Discharge Registers and questionnaires.
2. To elucidate the correlation between self-reported musculoskeletal symptoms and musculoskeletal diagnosis done by physicians.
3. To study the correlation of metabolic and genetic risk factors on knee and hip OA.

**MATERIAL AND METHODS**

Northern Finland 1966 Birth Cohort (NFBC1966) is an epidemiological and longitudinal research program designed to promote health and well-being of the population. It is comprised of mothers and newborns from the provinces of Oulu and Lapland with children’s expected date of birth in 1966 (12,068 mothers, 12,231 children). The prospective data forms a unique resource for the study of genetic, biological, social or behavioural risk factors in the incidence and progression of diseases. The data collection was started during mothers’ pregnancy and the children have been followed-up at the ages of 12 months, 14 years, 31 years, and 46 years. Clinical evaluation of musculoskeletal diseases has been undertaken as part of the last time-point study. Furthermore, extensive genetic data is available.

In this study, the epidemiology of OA of different joints at the ages of 31 and 46 will be described based on the Finnish National Hospital Discharge Registers. The occurrence of self-reported musculoskeletal symptoms will be investigated based on questionnaires. The correlation of diagnosed musculoskeletal disorders and self-reported symptoms will be studied.

We will also study the association of metabolic risk factors (BMI, hip-waist-ratio, fat percentage, lipid profile, glucose metabolism) with symptomatic knee and hip OA. We will further investigate whether we can identify genetic risk factors that contribute to both OA and metabolic disorders.

**DISCUSSION**

NFBC1966 gives an excellent opportunity to investigate the effects of different risk factors because subjects have been followed and data collected from the time before their birth. A study on the NFBC66 has shown, that 40% of male and 58.3% of female were overweight (BMI more than 25) already at the age of 31\(^5\). It is presumable that subjects that have developed OA already at the age of 46 have either strong risk factors or genetic susceptibility to the disease.

**REFERENCES**

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder suffered by 5–10% of women in reproductive age (1, 2). The etiology of PCOS remains unknown, though there is strong evidence of genetic component of this syndrome (3, 4). PCOS is characterized by oligoamenorrhea or amenorrhea, hyperandrogenism and hirsutism (2). Insulin resistance, obesity and anovulatory infertility are also common symptoms among PCOS-symptomatic women (5). In our previous population-based cohort study the women with self-reported oligoamenorrhea and hirsutism were found to have more infertility problems and smaller family size than non-symptomatic women at the age of 31 (6).

This is one of the few studies in which the impact of PCOS symptoms on lifetime reproductive success can be measured. In the present study, we took advantage of a large cohort of women at the end of their reproductive life span, as they turned 44 years in 2010. The primary aim of this study was to investigate the effects of symptoms of PCOS on reproductive performance (age at first delivery, family size and miscarriage rates) and to investigate whether women with self-reported oligoamenorrhea and hirsutism have a decreased family size and/or are more often childless than non-symptomatic women.

METHODS

The population of the study is derived from the prospective Northern Finland Birth Cohort 1966 (the NFBC1966), comprising all expected births from the year 1966 in the two northernmost provinces of Finland (n=12,058). Of them, 5889 were females. Enrollment in this database began at the 24th gestational week and so far data have been collected from the subjects at the ages of 1, 14 and 31 years.

A postal questionnaire including questions about oligoamenorrhea and hirsutism was sent to all women at the age of 31 (n=5608, response rate 81%, n=4535) and a clinical examination was performed (attendance rate 76.5%). Those who reported both hirsutism and oligoamenorrhea were defined as women with both symptoms (n=153). Data on pregnancies/deliveries were obtained from the Finnish Medical Birth Register (FMBR) in 2010 when the women were 44 years old.

RESULTS

Women with both symptoms had delivered at least one child as often as non-symptomatic women [75.2 versus
79.0%, adjusted odds ratio (OR) 0.86, 95% confidence intervals (CI) 0.57–1.30], were of similar age [mean (SD)] at first delivery [27.7 (4.81) versus 27.3 (4.71)] and had similar incidence of miscarriages (25.2 versus 23.3%). However, non-symptomatic women had more often ≥2 deliveries (61.6 versus 52.9%, adjusted OR 0.70, 95% CI 0.49–1.00, P=0.048) and had larger family size [mean (SD)] [2.4 (1.4) versus 1.9 (0.8), P<0.001]. Women with both symptoms had been treated more often for infertility than non-symptomatic women (6.1 versus 2.4%, adjusted OR 2.74, 95% CI 1.14–6.60, P=0.024).

**CONCLUSIONS**

In conclusion, the present study indicates that women with self-reported oligo-amenorrhea and hirsutism had their first child at the same age and were not more often childless when compared with non-symptomatic women in the same cohort. Women with both symptoms, however, had a smaller family size compared with non-symptomatic women and obese women with both symptoms had the worst prognosis as regards reproduction. This finding emphasizes the importance of lifestyle interventions to reduce the prevalence of obesity in this group of women. However, the impact of self-reported oligo-amenorrhea and hirsutism on fertility and family size was limited, suggesting that women with PCOS from infertility clinics represent a more severe phenotype than those from the general population.

All in all, the present findings are in line with our previous results at the age of 31 in this same cohort (1) and suggest that, even at more advanced age, women with both symptoms did not quite match the parity of healthy non-symptomatic women, and that infertility treatment did not always restore normal reproductive capacity in these women.

**REFERENCES**


