Northern Finland Birth Cohorts (NFBC)

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FINLAND IN FACTS

5.4 million

1.4 million inhabitants in metropolitan area

Life expectancy: year

Official languages are **FINNISH**... (spoken by 88.9%)

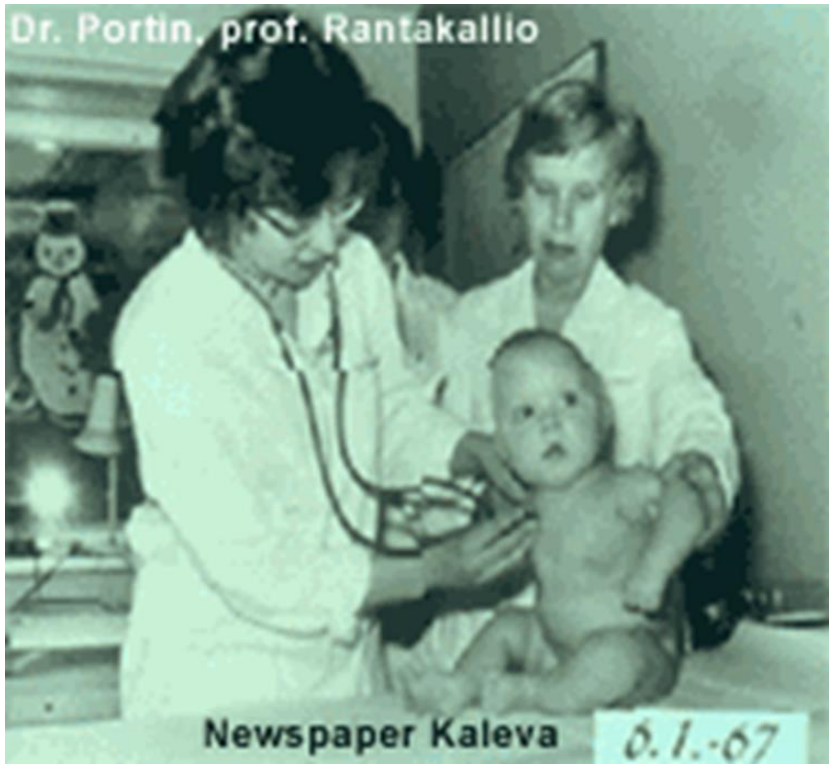
...and **SWEDISH** (spoken by 5.3%)

SÁMI is the mother tongue of about 1,900 people.

Christianity; 73.8% **LUTHERAN** and about 1.1% **ORTHODOX**

Northern Finland Birth Cohorts NFBC1966 and NFBC1986

- Risk factors involved in pre-term birth and intrauterine growth retardation
- Regional differences, social inequality – effect on subsequent morbidity



STUDY POPULATIONS

Mothers living in two northernmost provinces of Finland, Oulu and Lapland

- Northern Finland Birth Cohort Studies (NFBCs) - Population based prospective follow-up
- NFBC 1966 included all mothers with expected date of delivery between 1st of January to 31st December 1966
- NFBC 1986 included all mothers with expected date of delivery between 1st of July 1985 to 30 June 1986

NFBC 1966

MOTHERS:
12 068

CHILDREN:
12 231

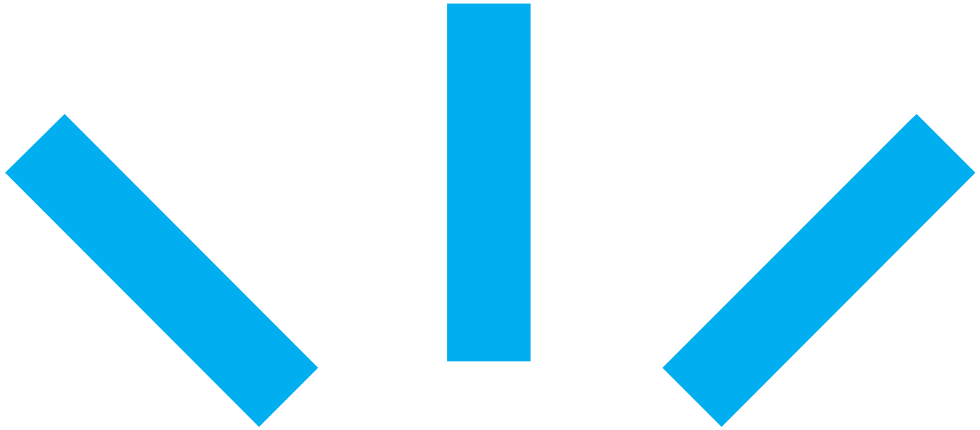
96 % of all births

NFBC 1986

MOTHERS:
9 362

CHILDREN:
9 479

99 % of all births

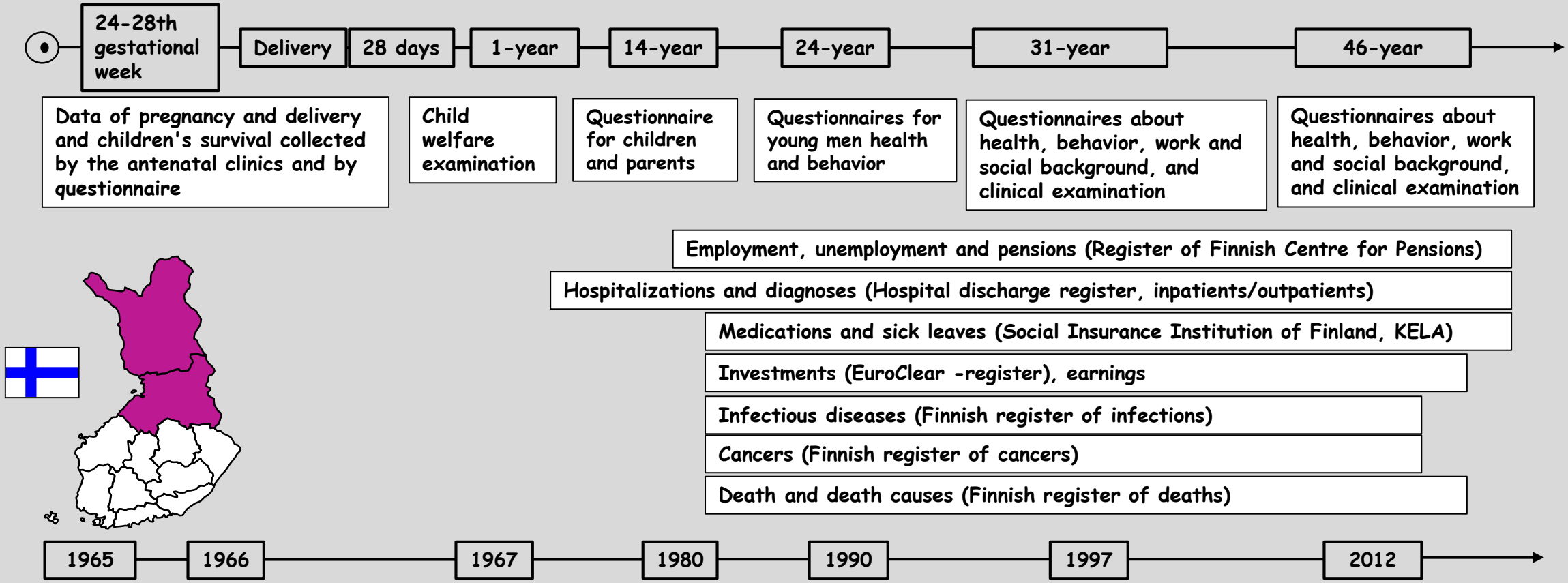


DATA COLLECTIONS

NFBC 1966

Northern Finland Birth Cohort 1966

12058 live-born children with expected date of birth 1.1.-31.12.1966



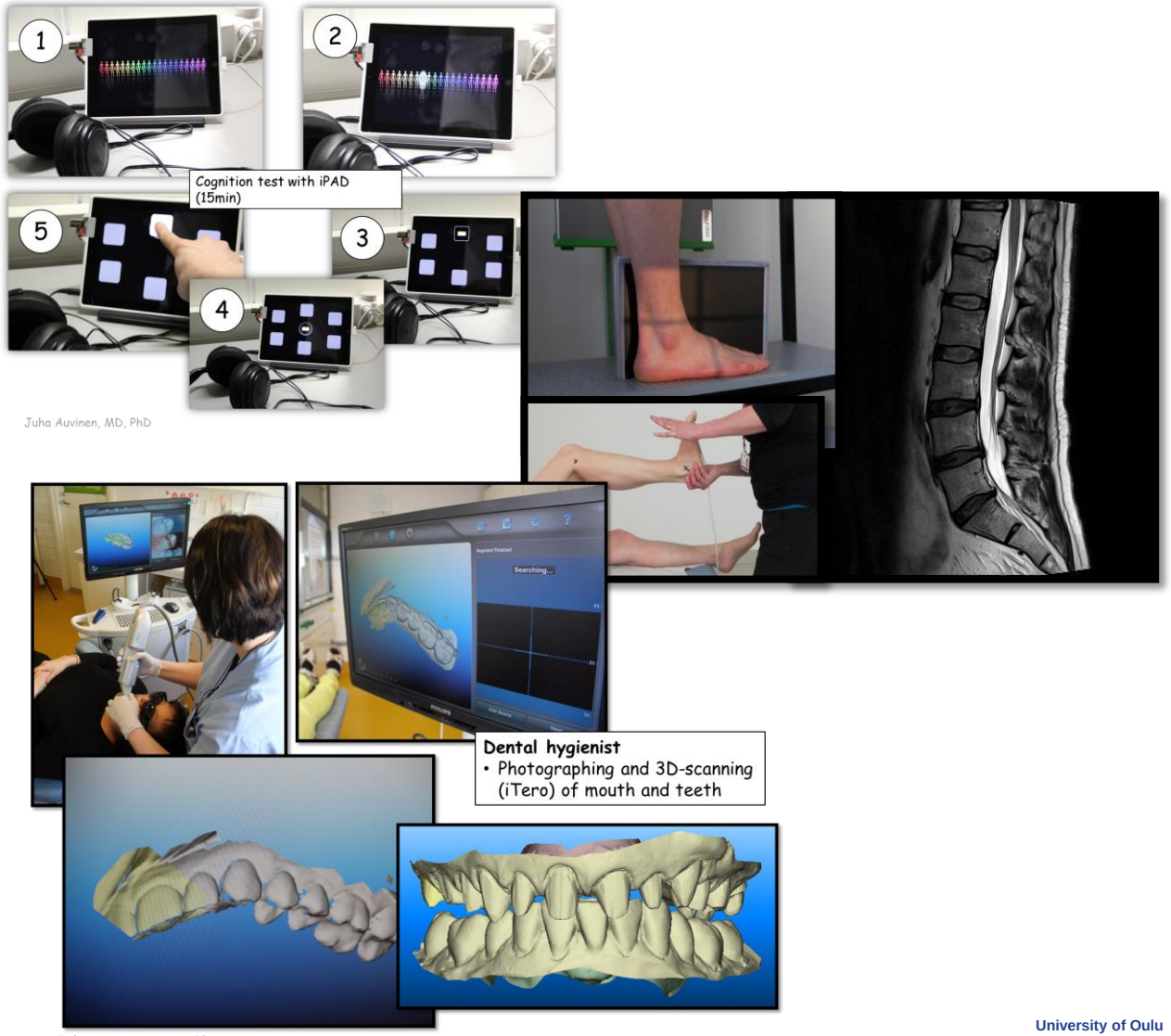
- By midwives at maternity health centers
- By self-administered questionnaires
- From hospital records and maternity health cards
- Clinical examinations, biological samples

Northern Finland Birth Cohort 1966:
Data collection at 45-46 years in 2012 - 2014

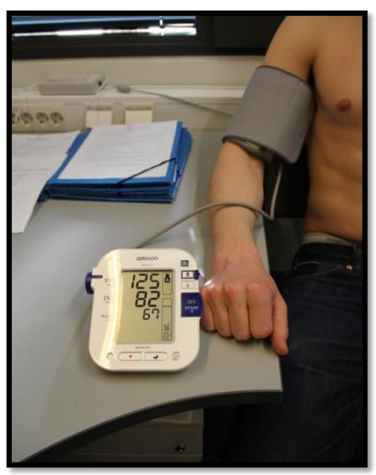
Health, behaviour, work and lifestyle
- Diet, FFQ
- Fittness/activity (objective)
- Weight, height, bioimpedance

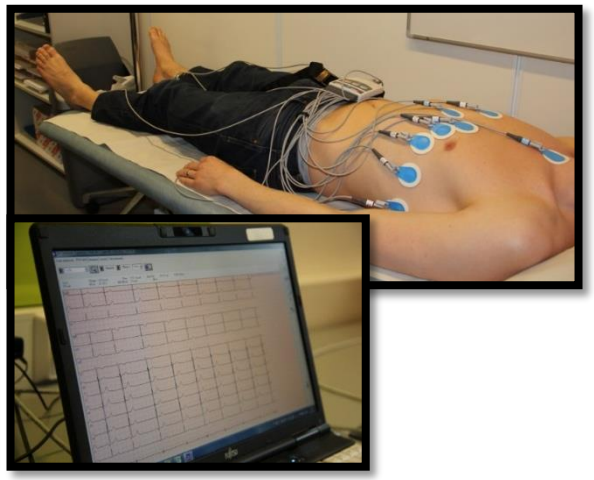
Cognitive, sensory, psychological/mental:
- Paired Associative Learning Test (PAL) using iPAD
- Vision/ eye tests
- [Hearing]

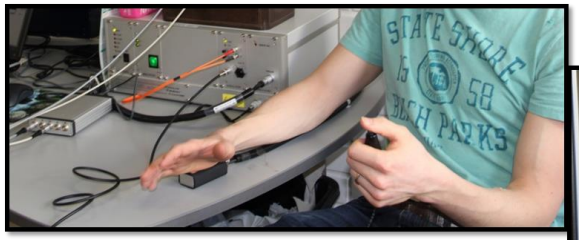
Musculoskeletal/dental:
- Muscle strength, spinal column position/posture (objective measure)
- Measures of osteoporosis
- Dental disorders

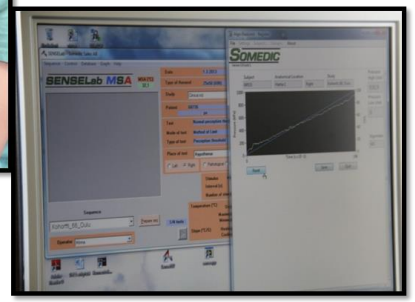


Northern Finland Birth Cohort 1966:
Data collection at 45-46 years in 2012 - 2014

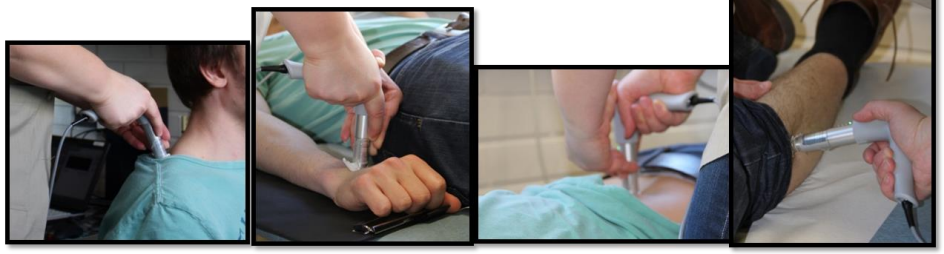








… Study nurse 5
- Thermal perception thresholds and tolerance
- Pressure pain threshold and tolerance



Cardiovascular
- BP (+central), heart and carotid artery ultrasound, ECG

Respiratory, lung function, atopy:
- Spirometry, skin prick tests

Gastro-intestinal:
- Kidney and liver function
- Chronic bowel inflammatory diseases

Urinary tract, reproductive:
- Menopausal symptoms
- Incontinence, prostatic symptoms

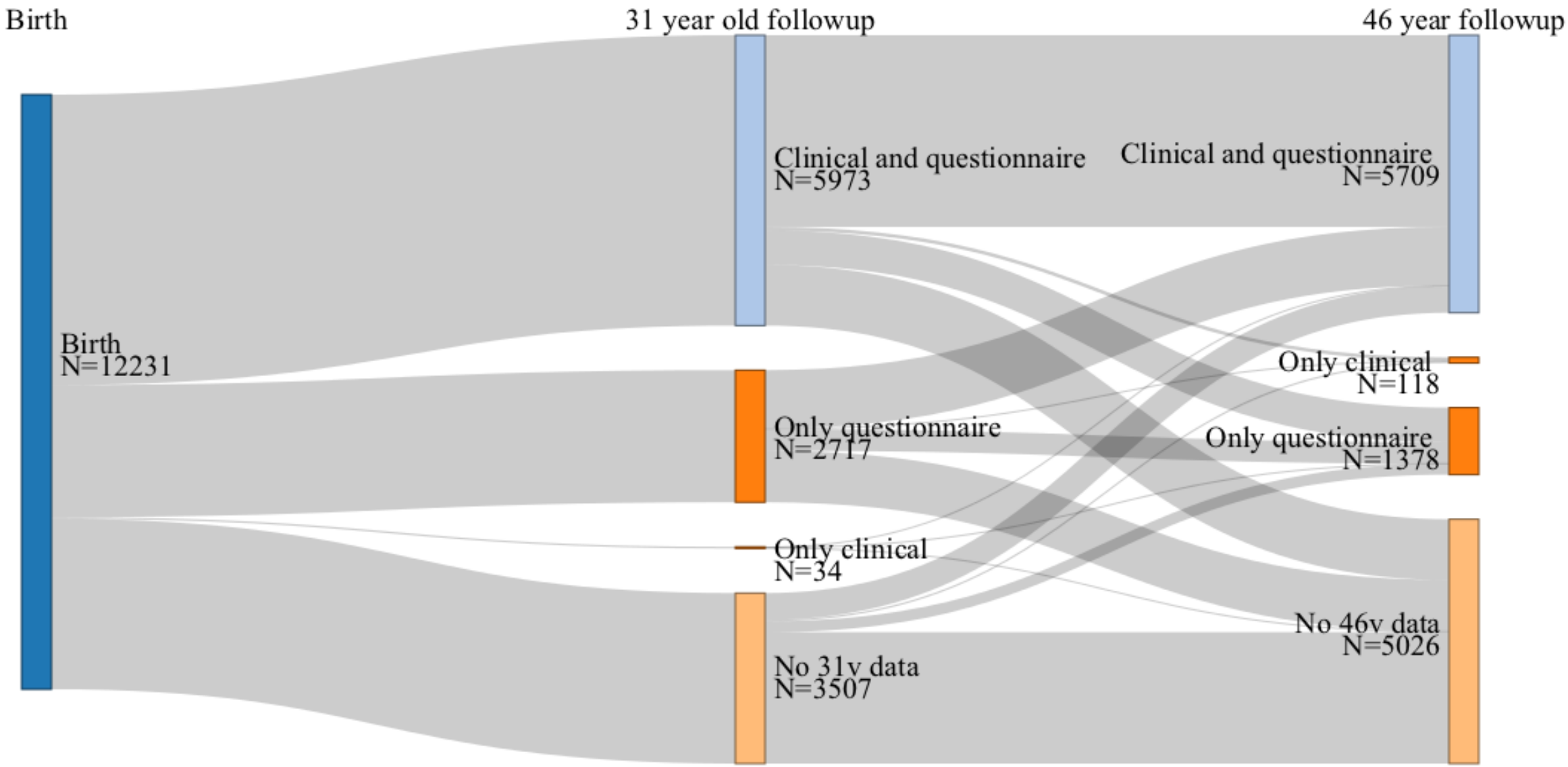
Blood and other samples: Measures of metabolic health, DNA, RNA, cells, urine, stool, saliva

POHJOIS-POHJANMAAN LIITTO
Council of Oulu Region
Vipuvoimaa EU:lta 2007–2013
Euroopan unioni
Euroopan aluekehitysrahasto
Euroopan sosiaalirahasto
University of Oulu

NFBC 1966 - psychiatric scales

	31 y	46 y
Anxiety & Depression – SCL	X	X
Anxiety & Depression – GHQ		X
Depression – BDI		X
Anxiety – GAD, STAI		X
Temperament – TCI	X	X
Alexithymia – TAS	X	X
Optimism – LOT	X	X
Schizotypy – SAS, PER, PAS, HPS	X	

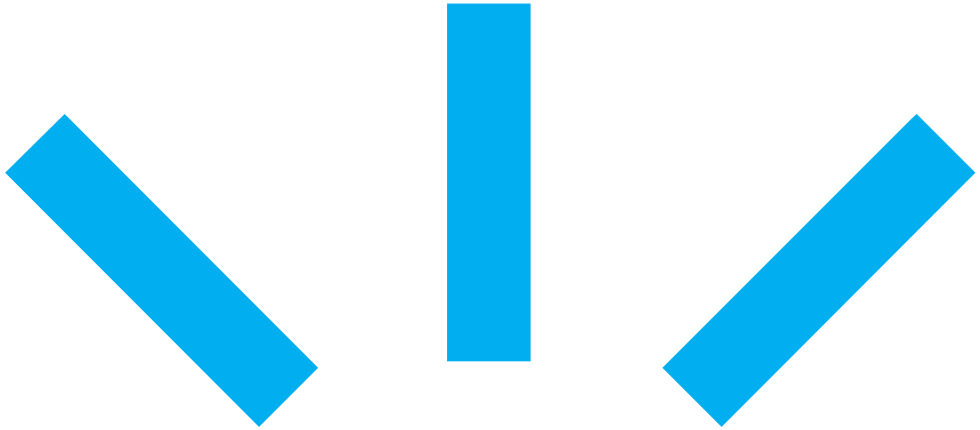
Northern Finland Birth Cohort 1966



Psychiatric subsamples (NFBC 1966)

- **Psychosis cases and controls (34y and 43y)**
- **sMRI, fMRI, DTI, rs-fMRI, cognitive tests, diagnostic interviews, PANSS, SOFAS, Strauss-Carpenter scale, family history, …**
- **Hospital note evaluation for lifetime psychiatric medication use**

- Huhtaniska S, et al. Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study. Psychiatry Res Neuroim 2017; 266:73-82.
- Hulkko AP, et al. Lifetime use of psychiatric medications and cognition at 43 years of age in schizophrenia in the Northern Finland Birth Cohort 1966. Eur Psychiatry 2017; 45:50-8.
- Moilanen JM, et al. Long-term antipsychotic use and its association with outcomes in schizophrenia - the Northern Finland Birth Cohort 1966. Eur Psychiatry 2016; 36:7-14.
- Nykänen S, et al. Use of psychiatric medications in schizophrenia and other psychoses in a general population sample. Psychiatry Res 2016; 235:160-8.



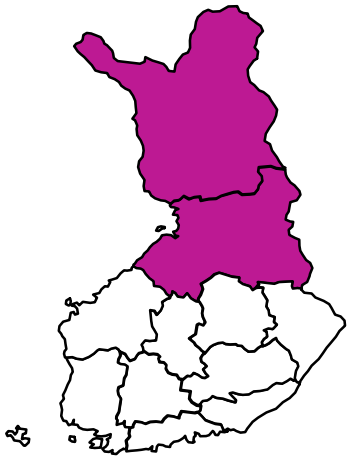
DATA COLLECTIONS

NFBC 1986

Northern Finland Birth Cohort 1986

9 479 live-born children with expected date of birth 1.7.1985-30.6.1986

10-16th gestational week	Delivery	1-year	7-8-year	15-16-year	24-year	Coming next... 33-year
Data of pregnancy and delivery and children's survival collected by the antenatal clinics and by questionnaire		Child welfare examination	Questionnaire for children and parents	Questionnaire for children and parents, clinical examination	Questionnaire for children (subpopulation), clinical examination	



Employment, unemployment and pensions (Finnish Centre for Pensions)

Hospitalizations and diagnoses (Care Register for Health Care)

Medications and sick leaves (Social Insurance Institution)

Infectious diseases (Finnish register of infections)

Cancers (Finnish register of cancers)

Death and death causes (Finnish register of deaths)

1985-1986	1986-1987	1992-1994	2000-2001	2009-2010	2018-2019

NFBC 1986 - psychiatric scales

	7-8 y	15-16 y
ADHD, Internalizing, Externalizing – Rutter B (parents)	X	
ADHD, Internalizing, Externalizing – Rutter A* (teachers)	X	
ADHD – SWAN (parents)		X
Internalizing, Externalizing – YSR (self-report)		X
Psychotic-like symptoms – PROD (self-report)		X
Alexithymia – TAS (self-report)		X

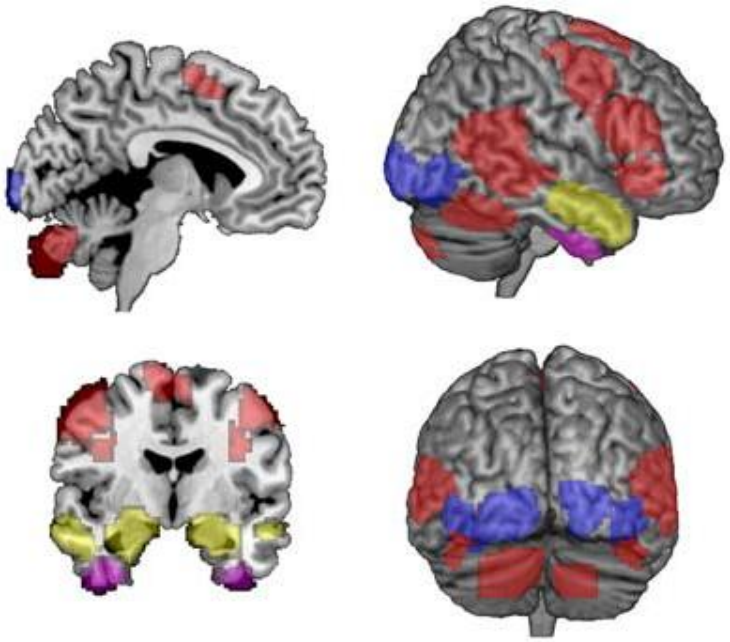
+ New data collection at age 32-33 y

Summary from addiction data (alcohol, tobacco, drugs) NFBC1986

- **REGISTER DATA**
  - Hospital data available until 2015 (outpatients since 1998)
  - Social benefits, medications
  - e.g. alcohol and drug use disorders
- **DATA FROM THE 15-16 -YEAR STUDY**
  - Detailed questionnaire data
  - smoking, drinking and use of intoxicants and drugs
- **PARENTAL SUBSTANCE USE**
  - Diagnoses, self-reports (during pregnancy and at children's age 15-16)

Miettunen J, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. Psychol Med 2014; 44:1727-38.

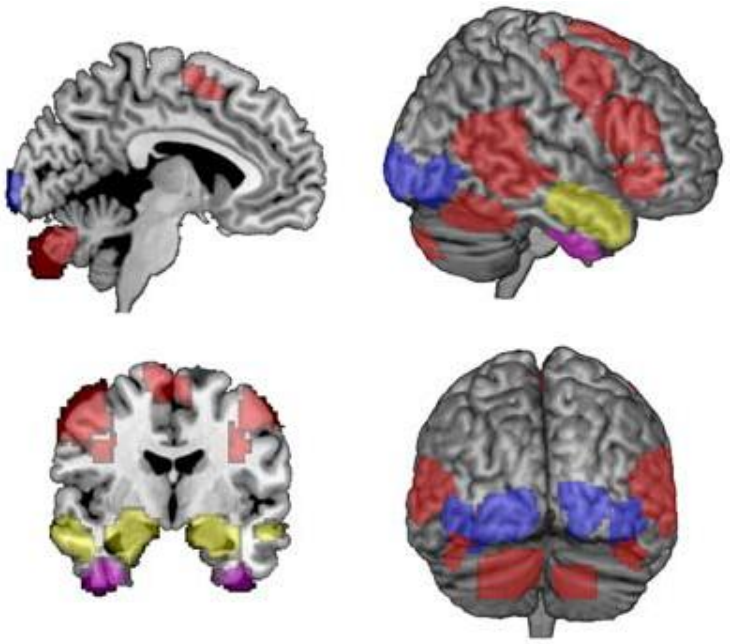
Psychiatric subsamples (NFBC 1986)



- **on ADHD (16-18y* and 22-24y**)**
- **on psychosis risk (22-24y)****
- **on maternal smoking (26y)*****
- **These include psychiatric interviews, questionnaires, cognitive tests, brain scanning, etc.**
- **References:**

- *Smalley SL, et al. Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. J Am Acad Child Adolesc Psychiatry. 2007; 46:1575-83.
- **Veijola J, et al. Young people at risk for psychosis: case finding and sample characteristics of the Oulu Brain and Mind Study. Early Interv Psychiatry. 2013; 7:146-54.
- ***Ramsay H, et al. Smoking in pregnancy, adolescent mental health and cognitive performance in young adult offspring: results from a matched sample within a Finnish cohort. BMC Psychiatry 2016; 16:430.

Brain imaging in psychiatric subsamples (NFBC 1986)

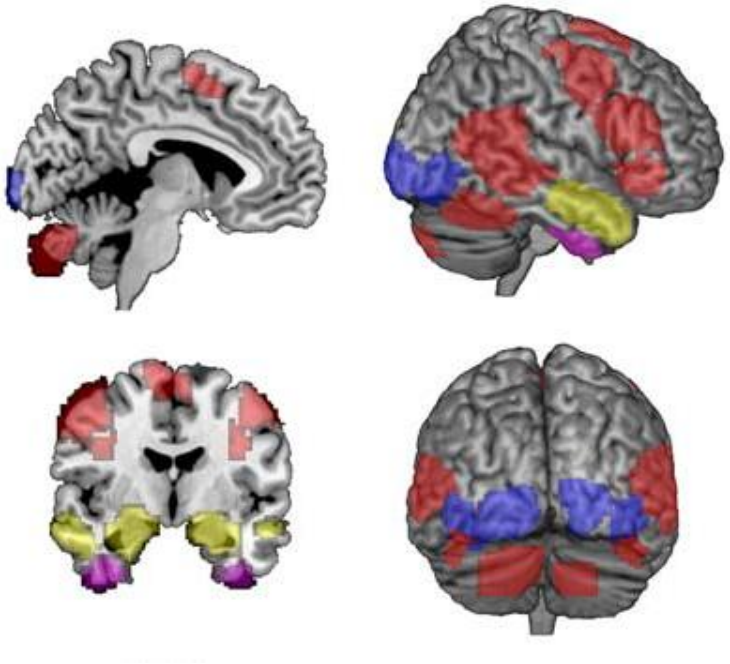


- **psychosis risk study (22-24y), n=329**
  - Structural MRI, diffusion-tensor imaging (DTI), resting state fMRI
  - Functional MRI: Sternberg verbal working memory task, Human Causal Learning prediction error task and facial recognition task
- **maternal smoking (26y), n=471**
  - MRI of the Brain (T2, DTI, MTR, R-fMRI)
  - MRI of abdomen (including kidneys and liver)

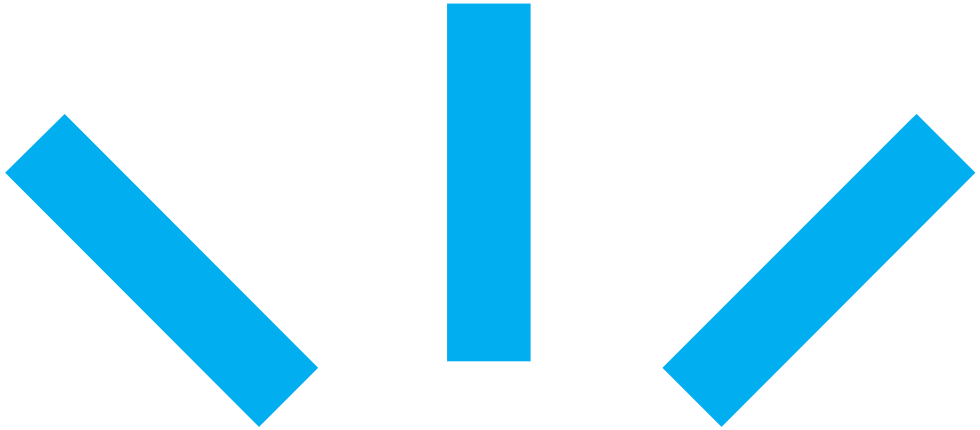
Lieslehto J, et al. Early adversity and brain response to faces in young adulthood. Human Brain Mapp 2017; 38:4470-8.

Björnholm L, et al. Structural properties of the human corpus callosum: Multimodal assessment and sex differences. Neuroimage. 2017; 152:108-118.

Cognition in psychiatric subsamples (NFBC 1986)



- **psychosis risk study (22-24y), n=329**
  - Cognitive tests: Vocabulary, Matrix Reasoning and Digit Span (WAIS III, Wechsler 1997), California Verbal Learning Test - Research Edition Logical Memory (WMS-R), Verbal fluency, Grooved Pegboard and Cambridge Neuropsychological Test Automated Battery (CANTAB) tests of Paired Associates Learning (PAL), Spatial Working Memory (SWM), Stockings of Cambridge (SOC), Rapid Visual Information Processing (RVP) and Information Sampling Test.
- **maternal smoking (26y), n=471**
  - Vocabulary, Matrix reasoning, Verbal fluency, Stroop, Pegboard, PAL in iPAD, SST in iPOD



REGISTER DATA

NFBC 1966 AND 1986

Data from different national registers

- Care Register for Health Care (inpatients, outpatients)
- Medications and sick leaves (Social Insurance Institution)
- Cancers, Infection diseases (specific registers)
- Employment, unemployment and disability pensions (Centre for Pensions)
- Investments (EuroClear -register), Earnings
- Marriages, born children, addresses, etc. (Population register)
- Causes of death (Finnish register of deaths; can be used only in Finland)
- Occupation, education (Statistics Finland; can be used only in Finland)
- Available death and hospital diagnoses also for parents
- THESE CAN BE USED FOR CASE FINDING, AS EXPOSURE, AS OUTCOME ETC.

Care Register for Health Care

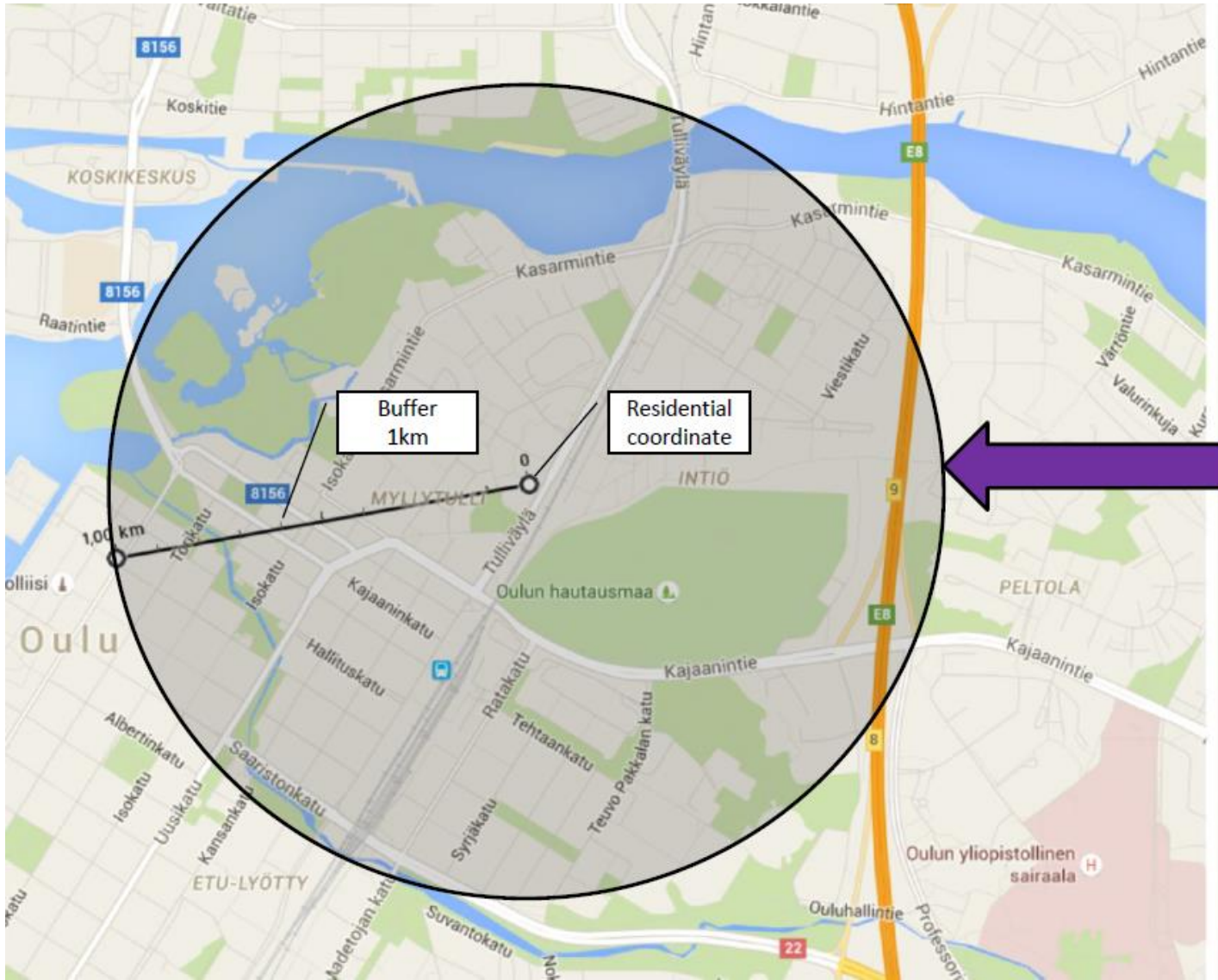
Miettunen J, et al. Use of register data for psychiatric epidemiology in the Nordic countries. In: Textbook in Psychiatric Epidemiology, 3rd edition, Eds. Tsuang M, Tohen M, Jones P, pp. 117-31. Wiley-Blackwell, 2011.

Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. Scand.J.Public Health 2012;40(6):505-515.

- **One of the oldest individual level hospital discharge registers covering the whole country (previously known as Hospital Discharge Register)**
- **Contains nationwide linkable data on all inpatient hospital discharges with personal identification** code **since 1969**
- **Outpatient visits in hospitals since 1998**
- **Outpatient primary care visits since 2011**
- **Diagnoses were recorded using**
  - ICD-8 during 1969−1986
  - ICD-9 during 1987−1995
  - ICD-10 since 1996
- **Intensively used for research purposes**
- **For statistical and research purposes the quality of FHDR has been shown to be at least satisfactory**

Geographical data

- Coordinate based migration history
- Postcode, grid (250x250m) or buffer based data



Geographic variables calculated within the buffer:

- Population density
- Number and type of apartments
- Number of different type of destinations
- Intersection density
- Number of public transportation stops
- Number of sport facilities
- Land use
- Greenness index
- Several socioeconomic variables
- Etc...

RESEARCH EXAMPLES

NFBC 1966 AND 1986

SCHIZOPHRENIA AND RELATED PSYCHOSES

- Various previous studies, appr. 85
- Mainly in the NFBC 1966
- Risk factors, brain imaging, cognition, outcomes, medication, genetics, suicidality, somatics, etc.

Jääskeläinen E, et al. Twenty years of schizophrenia research in the Northern Finland Birth Cohort 1966 – a systematic review. Schizophr Res Treatm 2015; 524875.

NFBC psychoses until 2016

NFBC1966 (n=11 923, alive at 16y) n=443, 3.7%

- Schizophrenia n=231, 1.9%
- Psychotic bipolar n=29, 0.2%
- Psychotic depression n=73, 0.6%
- Other psychoses n=110, 0.9%

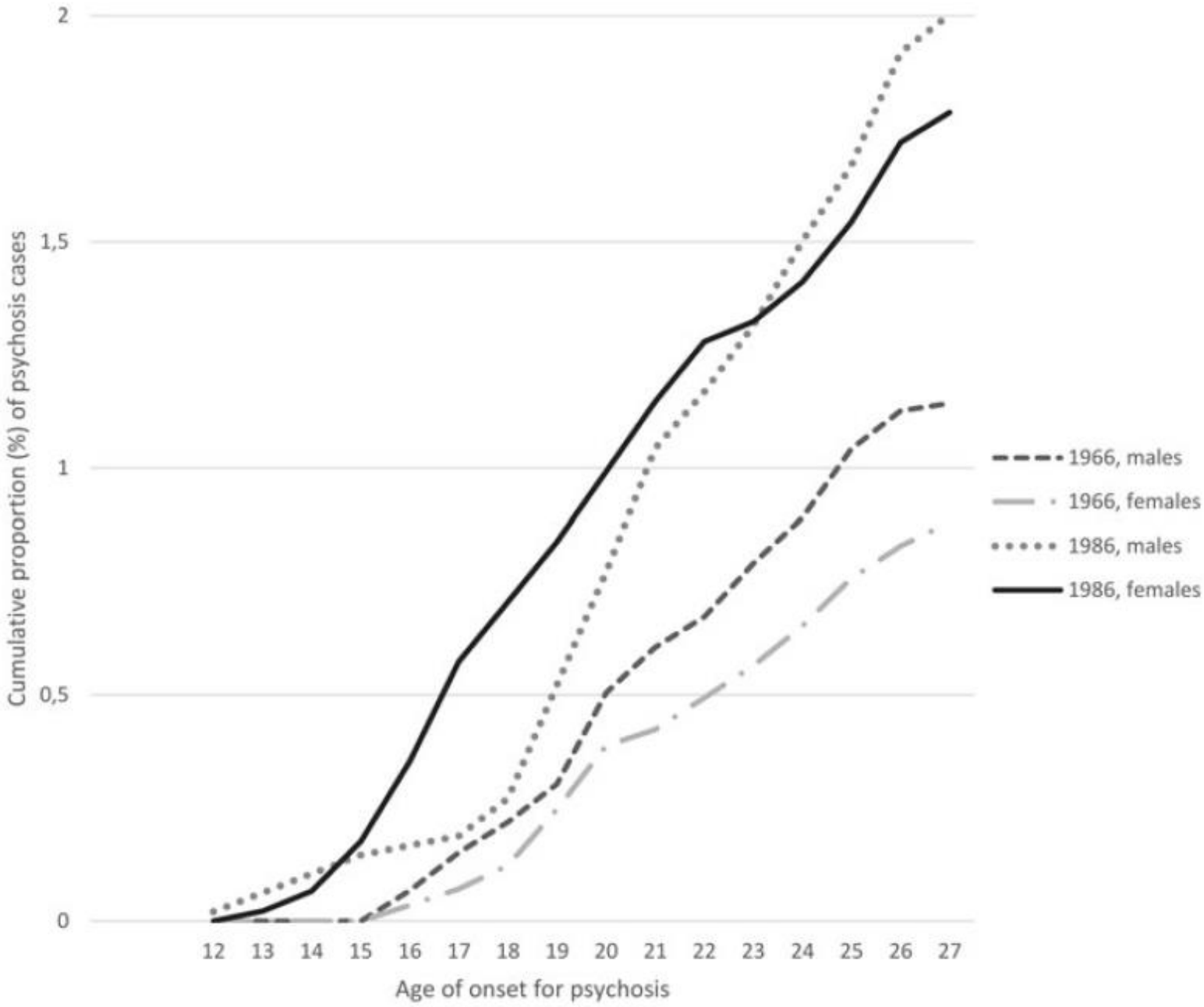
NFBC1986 (n=9 340, alive at 16y) n=222, 2.4%

- Schizophrenia n=74, 0.8%
- Psychotic bipolar n=19, 0.2%
- Psychotic depression n=31, 0.3%
- Other psychoses n=98, 1.0%

Filatova S, Marttila R, Koivumaa-Honkanen H, Nordström T, Veijola J, Mäki P, Khandaker GM, Isohanni M, Jääskeläinen E, Moilanen K, Miettunen J.

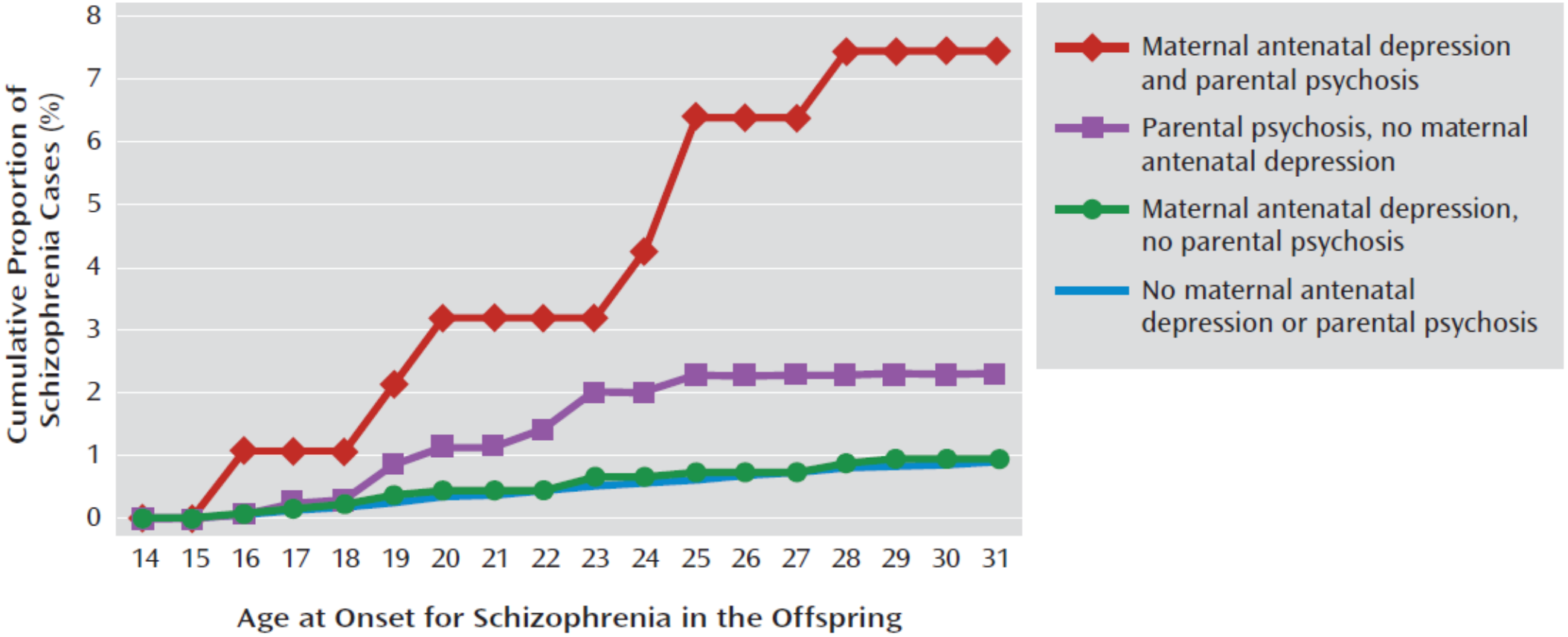
A comparison of the cumulative incidence and early risk factors for psychotic disorder in young adults in the Northern Finland Birth Cohorts 1966 and 1986.

Epidemiol Psychiatr Sci 2017; 26:314-324.



Mäki P, et al. Schizophrenia in the offspring of antenatally depressed mothers in the northern Finland 1966 birth cohort: relationship to family history of psychosis. Am J Psychiatry 2010;167:70-7.

FIGURE 1. Cumulative Incidence of Schizophrenia Among Offspring in the Northern Finland 1966 Birth Cohort by Maternal Mood During Pregnancy and Presence of Parental Psychosis



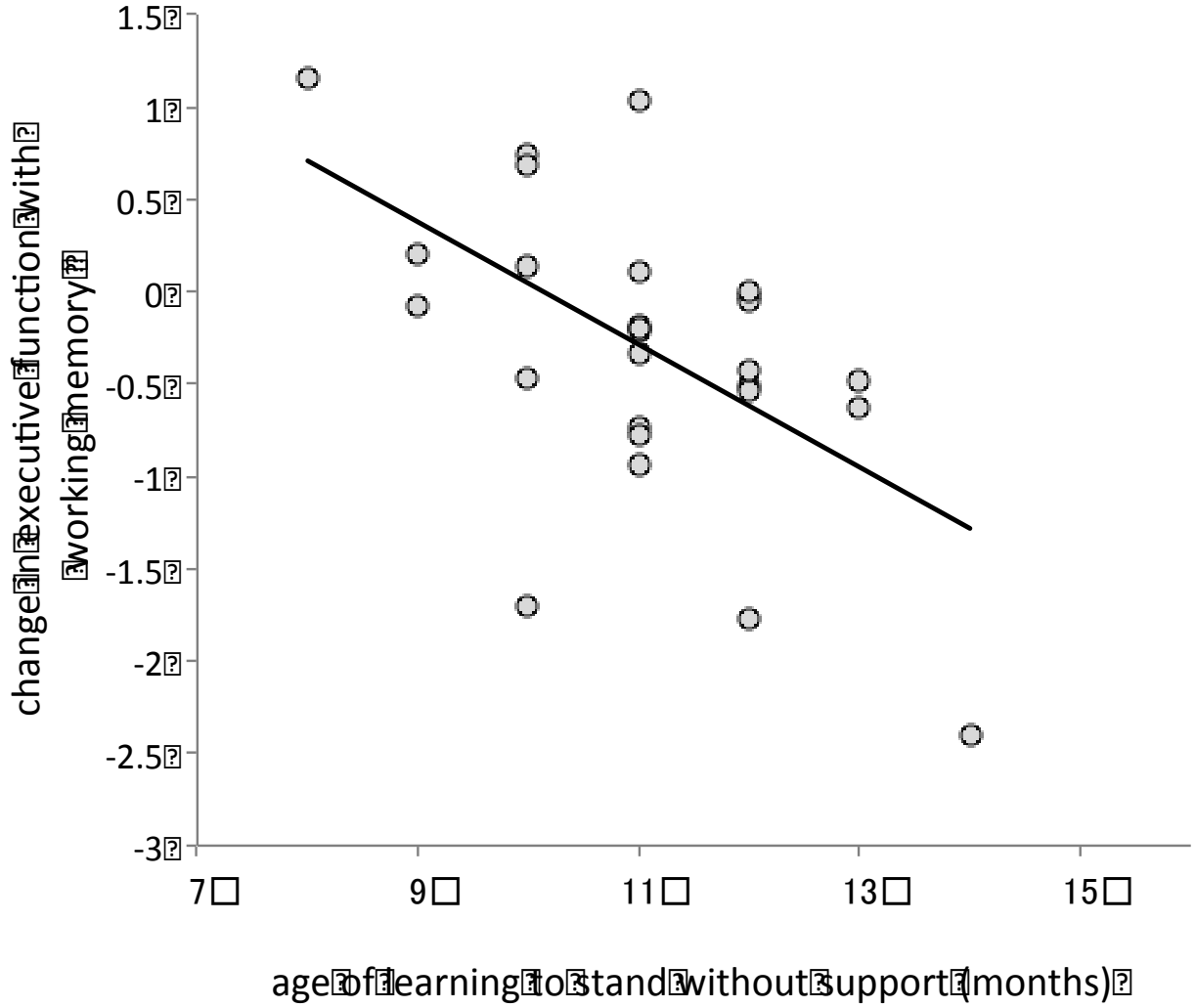
McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Järvelin MR, Chant D, Isohanni M.

Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study.

Schizophr Res. 2004; 67:237-45.

- The aim of this study was to explore the association between the use of vitamin D supplements during the first year of life and risk of developing schizophrenia.
- Subjects were drawn from the Northern Finland 1966 Birth Cohort (n=9,114).
- During the first year of life, data were collected about the frequency and dose of vitamin D supplementation.
- In males, the use of either irregular or regular vitamin D supplements was associated with a reduced risk of schizophrenia (Risk ratio (RR)=0.08, 95% CI 0.01-0.95; RR=0.12, 95% CI 0.02-0.90, respectively) compared with no supplementation.
- In males, the use of at least 2000 IU of vitamin D was associated with a reduced risk of schizophrenia (RR=0.23, 95% CI 0.06-0.95) compared to those on lower doses.
- There were no significant associations between either the frequency or dose of vitamin D supplements and (a) schizophrenia in females, nor with (b) nonpsychotic disorder or psychotic disorders other than schizophrenia in either males or females.

Significant negative correlation between the change in executive function with working memory from aged 34 to 43 and age at learning to stand in infancy in subjects with schizophrenia.



Kobayashi H, Isohanni M, Jääskeläinen E, Miettunen J, Järvelin M-R, Veijola J, Jones PB, Murray GK.

Linking the developmental and degenerative theories of schizophrenia: association between infant development and adult cognitive decline.

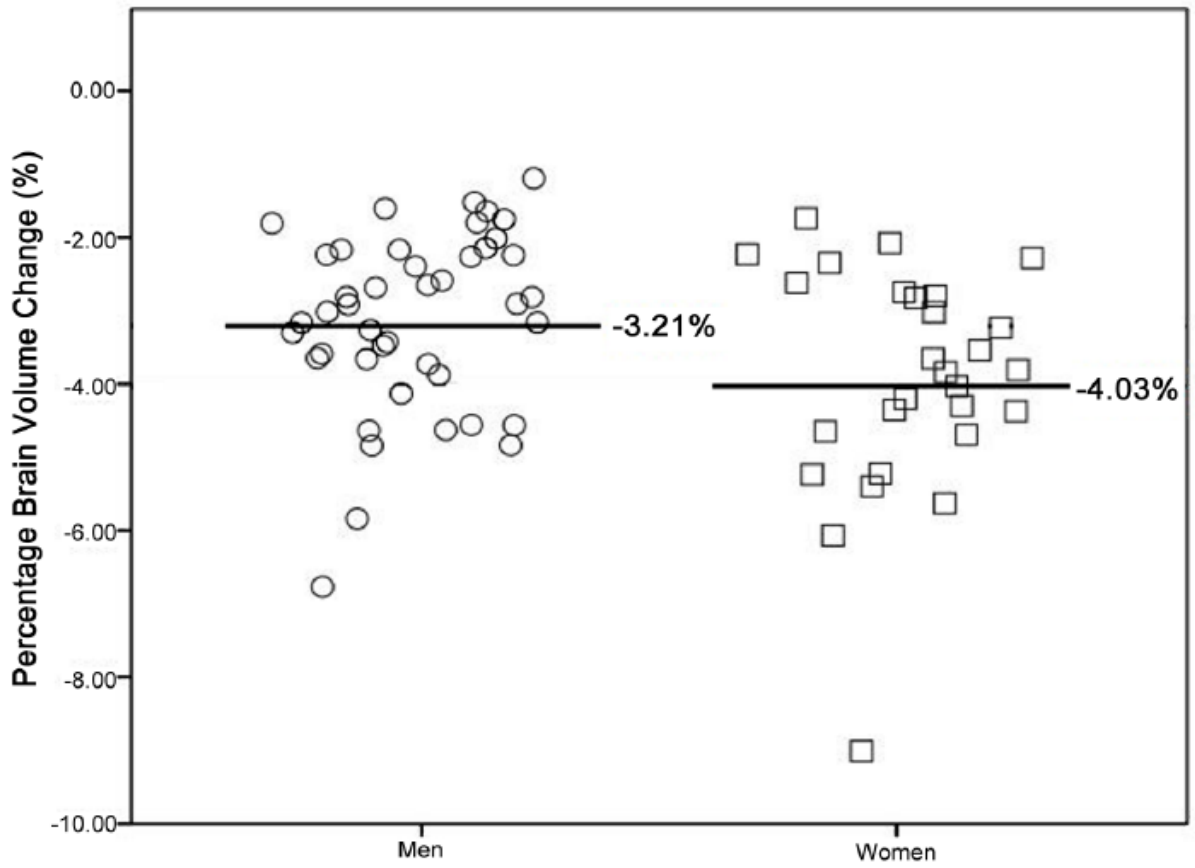
Schizophr Bull 2014; 40:1319-27.

Guo JY, Isohanni M, Miettunen J, Jääskeläinen E, Kiviniemi V, Nikkinen J, Remes J, Huhtaniska S, Veijola J, Jones PB, Murray GK.

Brain structural changes in women and men during midlife.

Neurosci Lett. 2016; 615:107-12.

Fig. 2. Sex differences in regional brain edge structural changes over time after controlling for total brain loss: women showed greater regional brain reduction compared with men on the edges of the bilateral frontal lobe, bilateral parietal lobe and bilateral occipital pole (shown in yellow and red), and less regional brain reduction than men on the edges of the bilateral precentral gyri, bilateral paracingulate gyri and supplementary motor cortices (shown in blue).



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

Hulkko AP, Murray GK, Moilanen JM, Haapea M, Rannikko I, Jones PB, Barnett JH, Huhtaniska S, Isohanni M, Koponen H, Jääskeläinen E, Miettunen J.

Lifetime use of psychiatric medications and cognition at 43 years of age in schizophrenia in the Northern Finland Birth Cohort 1966.

Eur Psychiatry 2017; 45:50-8.

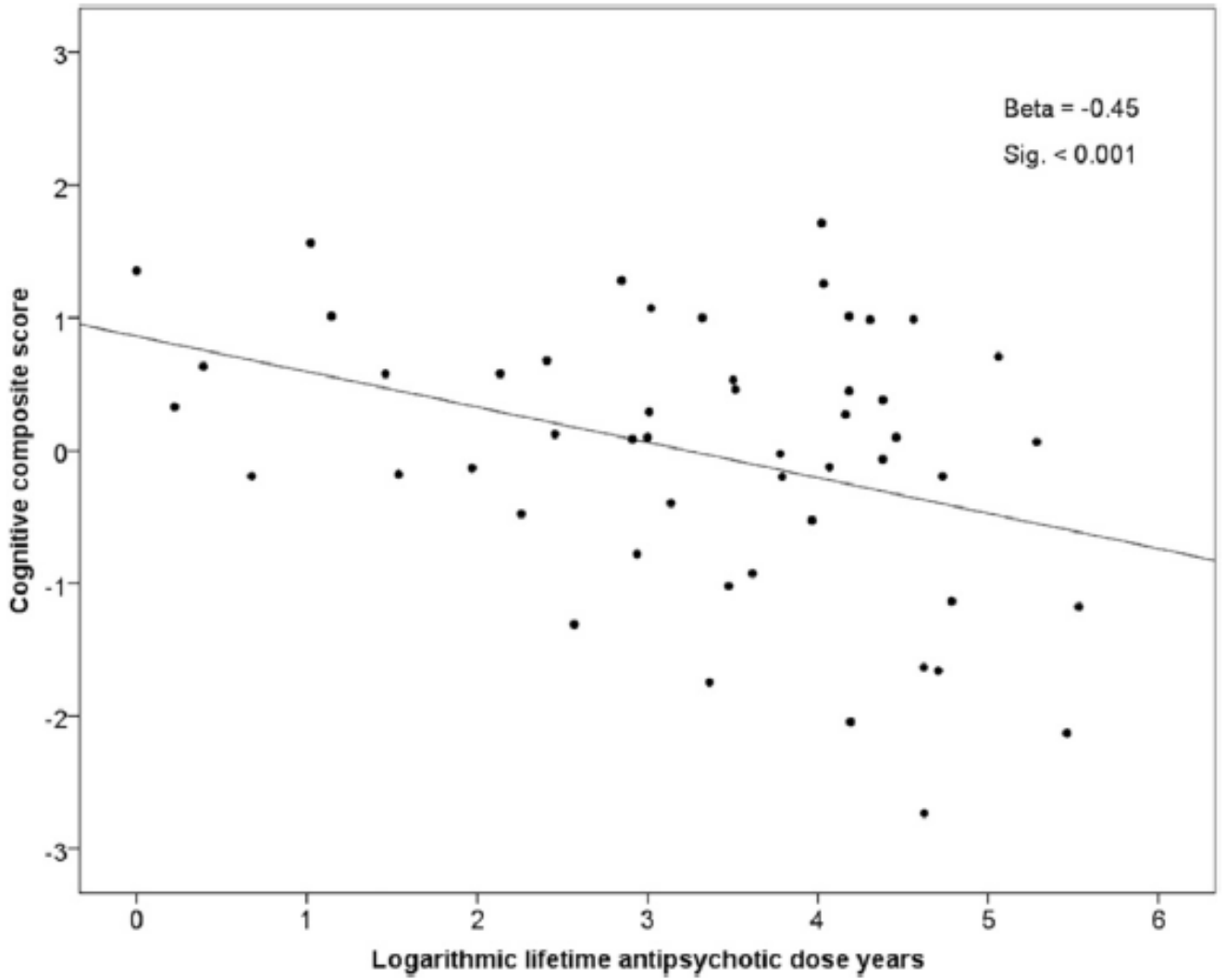


Fig. 1. The association between lifetime dose-years of any antipsychotics and cognitive composite score at age 43 years in schizophrenia. *Higher lifetime antipsychotic dose-years associated with poorer cognitive composite score*. (Beta coefficient and statistical significance are from linear regression analysis with natural logarithm of dose-years of any antipsychotics as the predictor variable).

Huhtaniska S, Jääskeläinen E, Heikka T, Moilanen JS, Lehtiniemi H, Tokka J, Manjón JV, Coupé P, Björnholm L, Koponen H, Veijola J, Isohanni M, Kiviniemi V, Murray GK, Miettunen J.

Long-term antipsychotic and benzodiazepine use and brain volume changes in schizophrenia: The Northern Finland Birth Cohort 1966 study.

Psychiatry Res Neuroim 2017; 266:73-82.

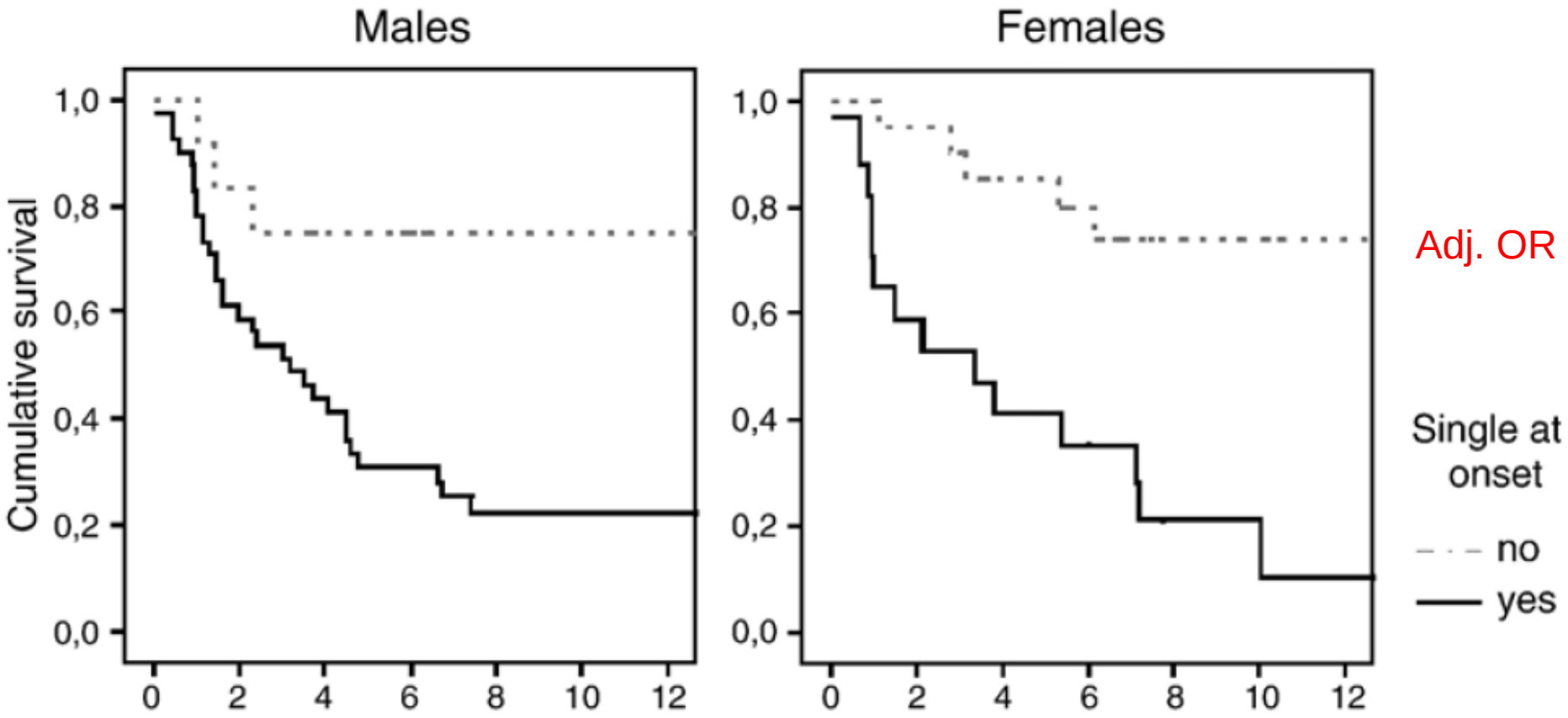
- 69 controls and 38 individuals with schizophrenia underwent brain MRI at the ages of 34 and 43 years.
- Brain structures were delineated using an automated volumetry system, volBrain

Table 4.2
Associations between antipsychotic dose and benzodiazepine dose and brain structural change during the follow-up and the statistically significant associations of antipsychotic dose, benzodiazepine dose, PANSS average score and hospitalization days during the follow-up in the same model. ICV and sex as covariates in all analyses. Statistically significant (p < 0 05) findings are in **bold**.

Brain area	CPZy	BZDy	CPZy, BZDy, PANSS and hospitalization days in the same model
Total Brain	b = -0.269 p = 0.088	**b = -0.346** **p = 0.037**	BZDy b = -0.091 p = 0.716
Total GM	**b = -0.380** **p = 0.012**	b = -0.151 p = 0.367	CPZy b = -0.229 p = 0.283
Cerebrum	b = -0.261 p = 0.092	**b = -0.324** **p = 0.048**	BZDy b = -0.095 p = 0.702
Cerebrum GM	**b = -0.387** **p = 0.012**	b = -0.152 p = 0.376	CPZy b = -0.239 p = 0.271
Lateral ventricles	**b = 0.458** **p = 0.003**	**b = 0.355** **p = 0.037**	**CPZy** **b = 0.487 p = 0.035** BZDy b = 0.037 p = 0.879
Caudate	b = -0.294 p = 0.062	**b = -0.489** **p = 0.002**	BZDy b = -0.350 p = 0.141
Putamen	b = -0.303 p = 0.074	b = -0.266 p = 0.144	n.s.
Thalamus	**b = -0.344** **p = 0.030**	**b = -0.360** **p = 0.033**	CPZy b = -0.153 p = 0.500 BZDy b= -0.052 p = 0.832
Hippocampus	**b = -0.340** **p = 0.040**	b = -0.184 p = 0.306	CPZy b = -0.245 p = 0.214 **hospitalization days b = -0.788** **p < 0.001**
Accumbens	**b = -0.378** **p = 0.018**	**b = -0.404** **p = 0.018**	CPZy b = -0.072 p = 0.754 BZDy b = -0.180 p = 0.468

CPZy = antipsychotic dose years in chlorpromazine equivalents during follow-up, BZDy = benzodiazepine dose years in defined daily dose during follow-up, ICV = intracranial volume, GM = grey matter, b= standardized beta, PANSS= The average score of Positive and Negative Syndrome Scale (PANSS) total score at 34 years and 43 years, n.s. = non-significant.

Miettunen J, et al. Socio-demographic and clinical predictors of occupational status in schizophrenic psychoses--follow-up within the Northern Finland 1966 Birth Cohort. Psychiatry Res. 2007;150:217-25.



Adj. OR 6.5 (1.8-23.1)

YEARS FROM FIRST HOSPITAL ADMISSION TO DISABILITY PENSION

Vladimirov D, Niemelä S, Auvinen J, Timonen M, Keinänen-Kiukaanniemi S, Ala-Mursula L, Laitinen J, Miettunen J.

Changes in alcohol use in relation to sociodemographic factors in early midlife.

Scand J Publ Health 2016; 44:249-57.

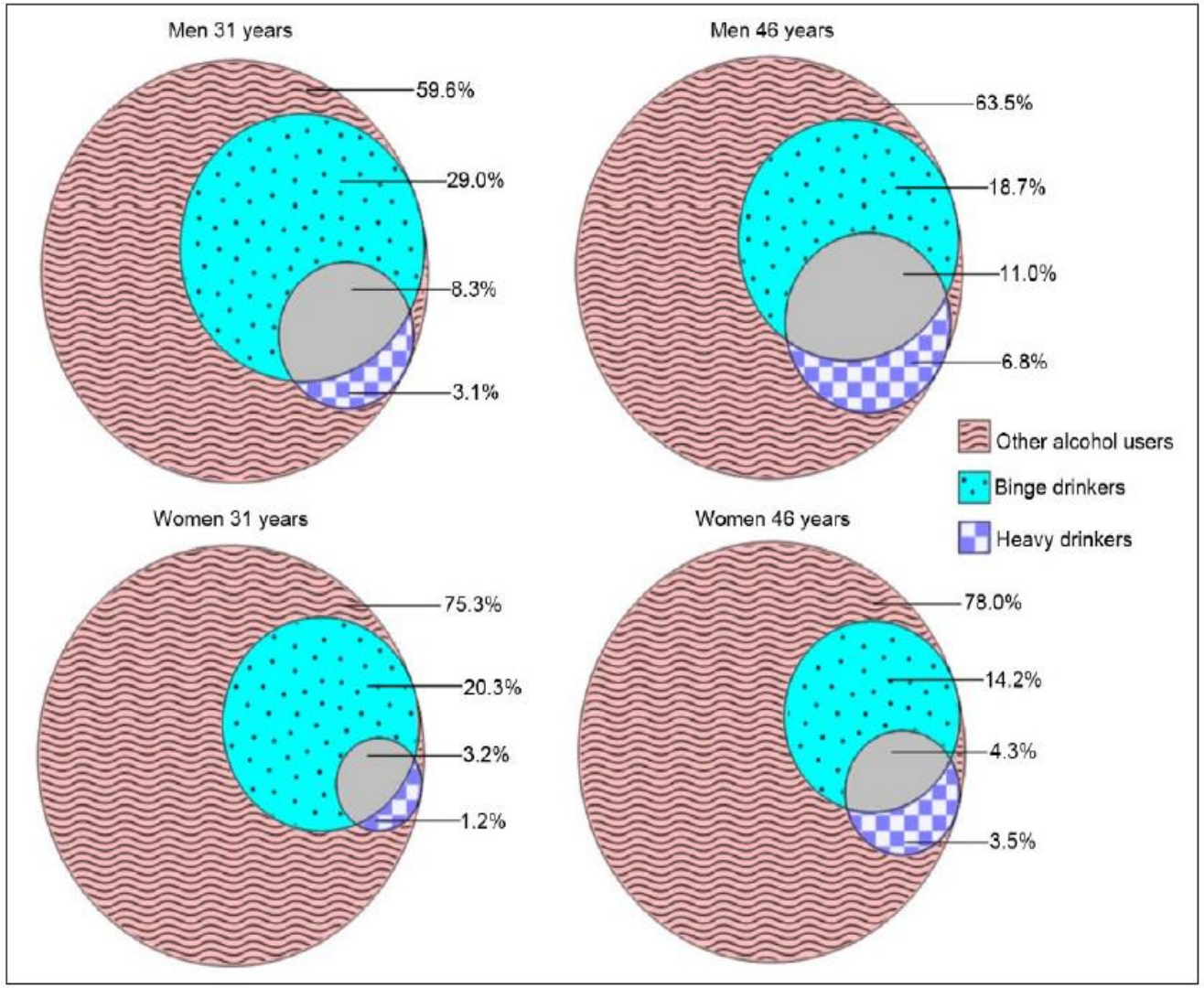


Figure 2. Venn diagrams of alcohol user subtypes at ages 31 and 46 years.

Substance use and psychosis risk – NFBC1986

- NFBC1986 (N=6,258), follow-up from age 16y until 28y
- The risk of psychosis was elevated in subjects who had tried **cannabis** 5 times or more (HR=5.2; 95%CI=2.1-12.9). The association remained statistically significant even when adjusted for prodromal symptoms, parental psychosis and gender (HR=2.9, 1.2-7.6).
- Heavy **tobacco** use increased risk of subsequent psychosis (HR = 4.7, 95% CI 2.5-8.6). When adjusted for prodromal symptoms the association persisted (HR = 3.1, 1.9-4.9) and remained significant even after adjustments with multiple known risk factors.
- Compared to those who had never used inhalants, those using **inhalants** had increased risk of incident psychosis with most frequent inhalant use associated with the greatest risk (unadjusted HR=9.5; 3.9-23.2). After adjusting for baseline psychotic experiences, other substance use and parental substance abuse, the risk of psychosis persisted (HR=3.7; 1.2-11.2).

Doctoral student:
Antti Mustonen

Parental somatic illnesses – NFBC 1986

- NFBC1986 (N=9,1377), parental diagnoses before offspring age 18y
- Several associations when unadjusted. After controlling for covariates the results remained statistically significant in terms of the father's diagnosis of neoplasms (OR 2.75, 95% CI 1.35-5.62, p=0.006), and those relating to factors influencing health status and contact with health services (OR 2.66, 95% CI 1.35-5.27, p=0.005).
- When we predicted children's psychotic like symptoms, only parental musculoskeletal disorders associated with higher proportion of symptoms.
- More and stronger associations between parental somatic illnesses and other psychiatric symptoms (Youth Self Report) of the offspring.

Räsänen S, et al. Parental hospital-treated somatic illnesses and psychosis of the offspring – the Northern Finland Birth Cohort 1986 Study, Early Interv Psychiatry, in press.

Post-doc researchers:
Mika Niemelä and
Sami Räsänen

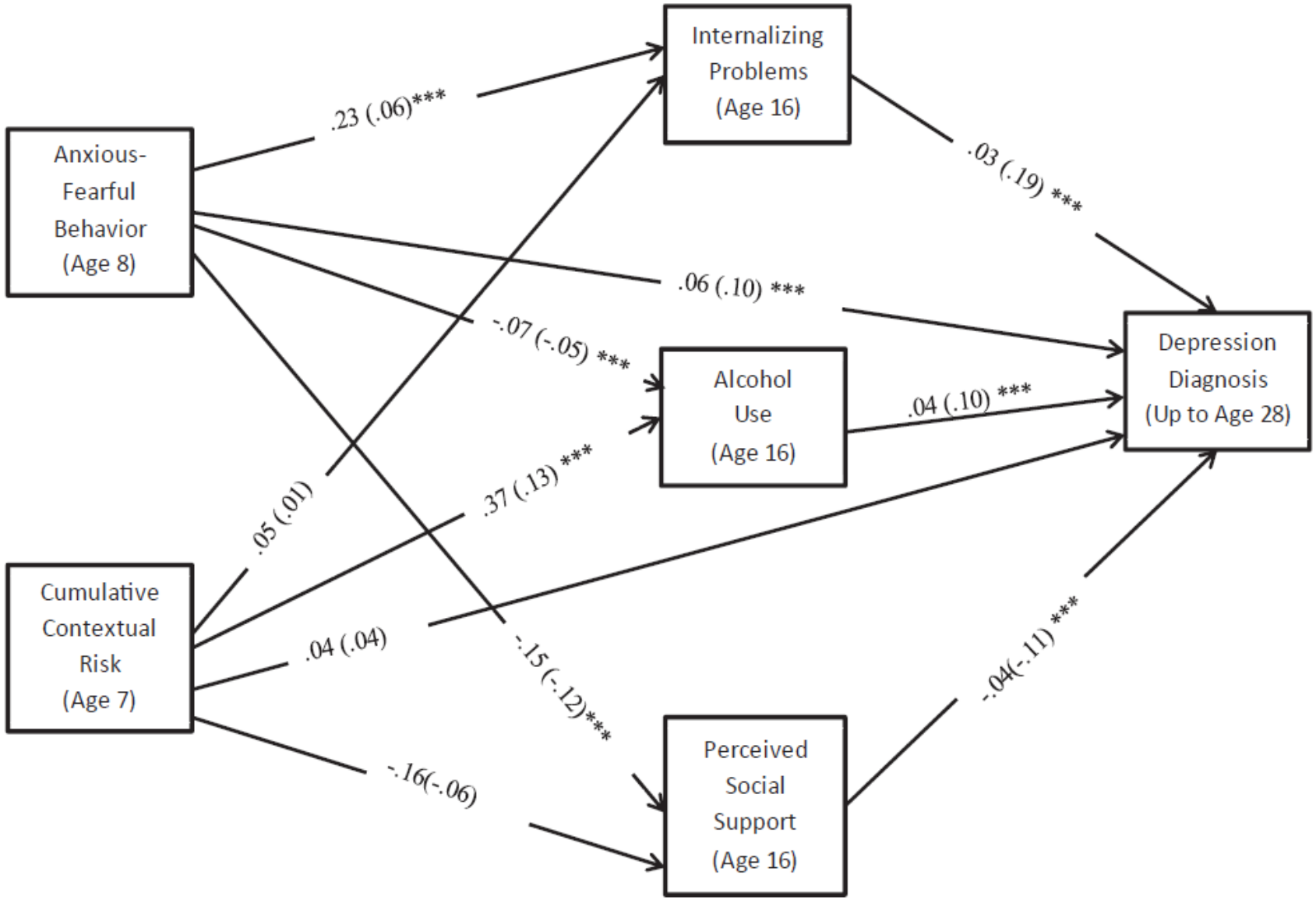
Doctoral student:
Lotta Kinnunen

NFBC 1986

Patwardhan I, Mason WA, Savolainen J, Chmelka MB, Miettunen J, Järvelin M-R.

Childhood cumulative contextual risk and depression diagnosis among young adults: The mediating roles of adolescent alcohol use and perceived social support.

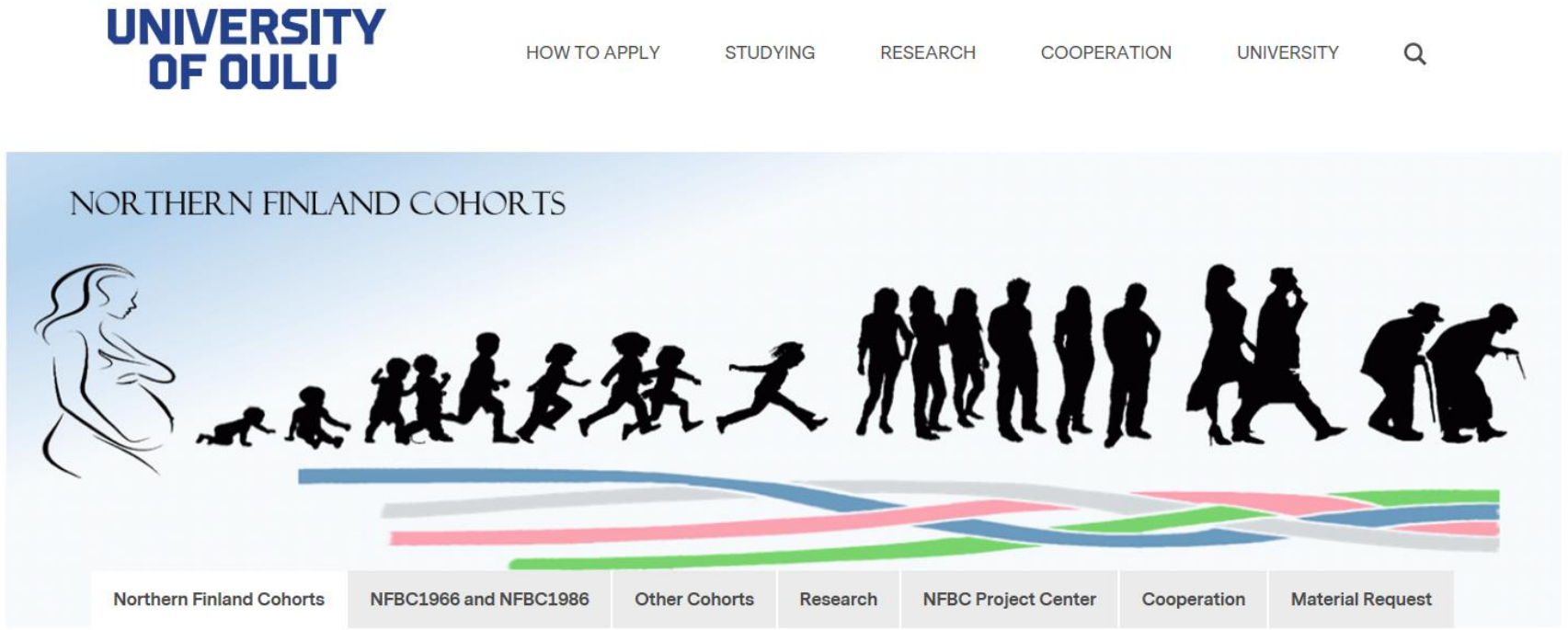
J Adolesc 2017; 60:16-26.



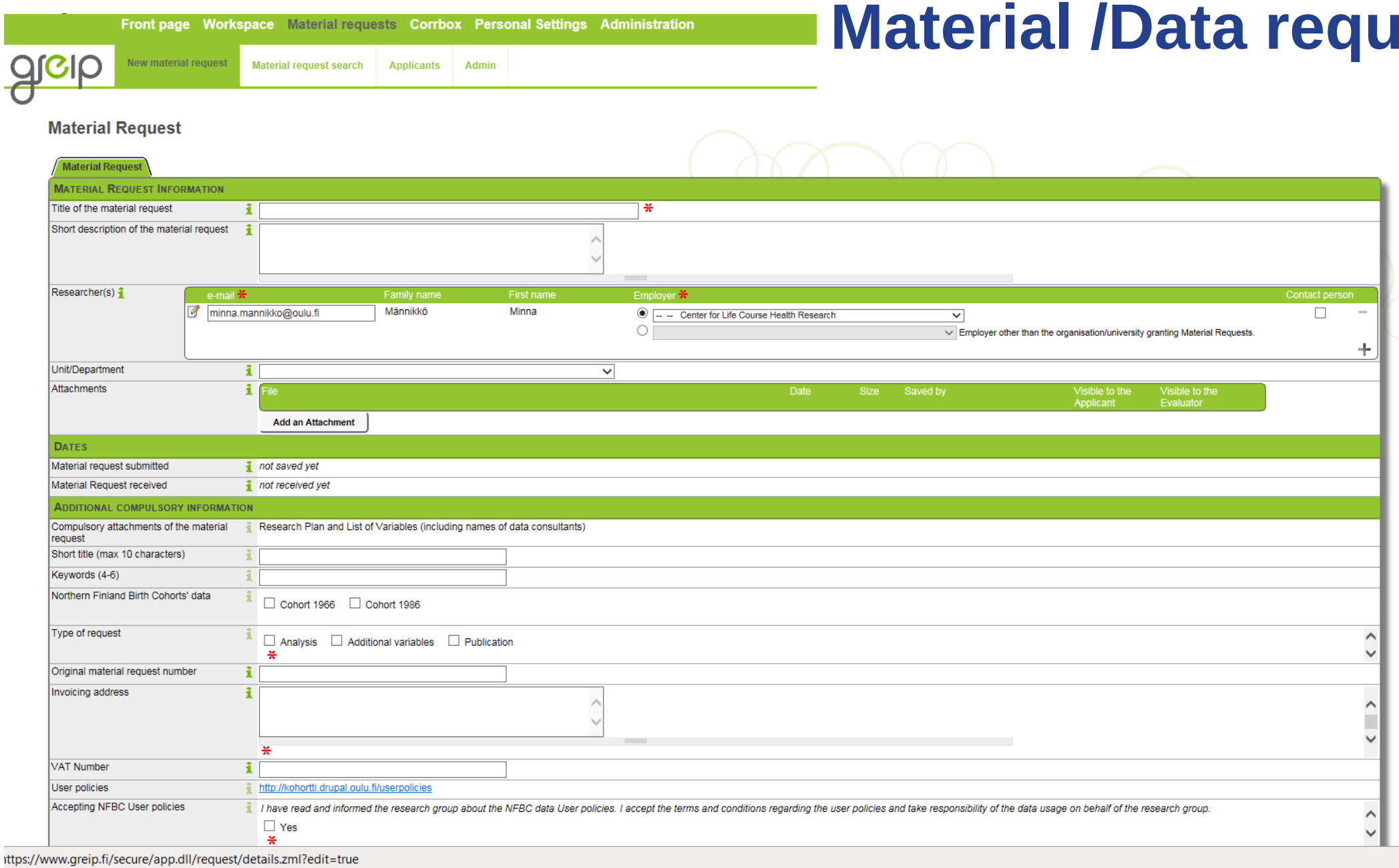
MATERIAL REQUEST

NFBC 1966 AND 1986

NFBC web pages: www.oulu.fi/nfbc



Material /Data request



https://www.greip.fi/secure/app.dll/request/details.zml?edit=true

Additional data permission issues

- Include a study plan and variable list
- Data Transfer Agreement
- European Commission Clauses agreement
- Some registers (cases of death, occupation, education) not available for researchers outside Finland or European Union
- Permission usually in a couple of weeks, getting data may take some time, active collaboration helps ☺

- **MOST OF THE DATA IS AVAILABLE FOR EVERYONE!!!**

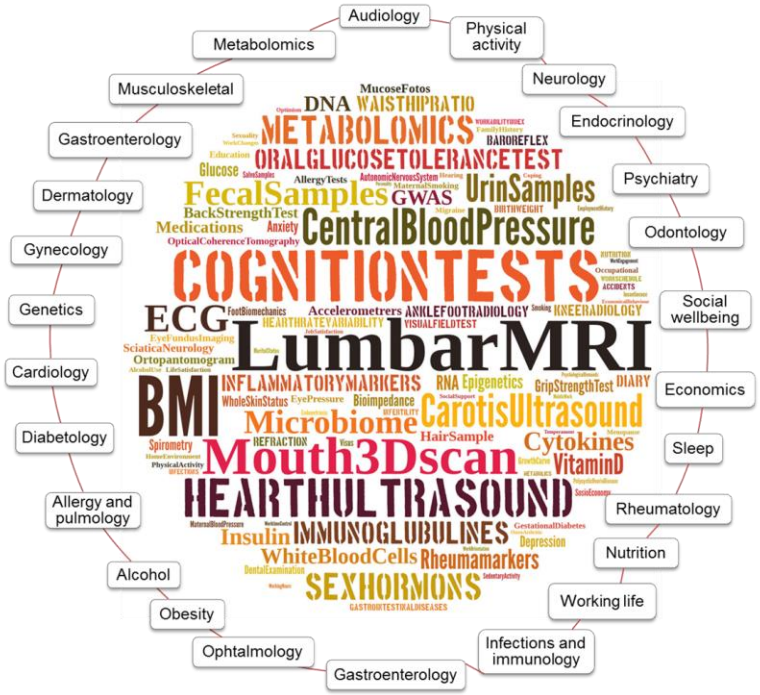
Statistics from 2013-2015

Distribution of data requests

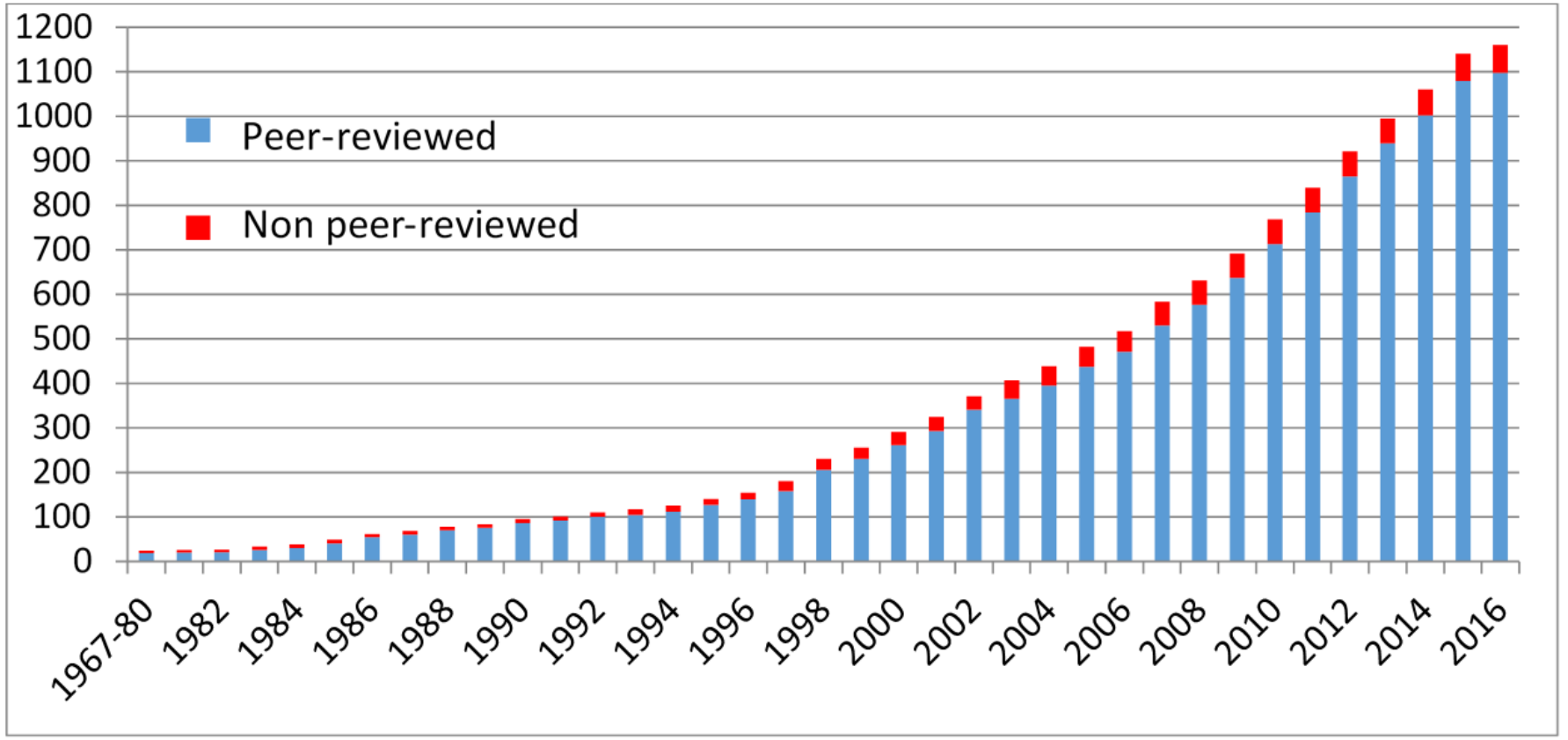
- Approximately 90 applications per year

	2013	2014	2015
Oulu University	55.0 %	60.4 %	70.2 %
Other domestic	14.6 %	18.5 %	10.4 %
International	30.3 %	21.0 %	19.5 %

- 700 registered users
- National 65%, International 35 %



Cumulative number of publications with NFBC data since 1967



- Publications and theses listed in the webpage (www.oulu.fi/nfbc)

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THANK YOU AND WELCOME TO OULU!

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