Northern Finland Birth Cohorts (NFBC)

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FINLAND IN FACTS

5.4 million

1.4 million inhabitants in metropolitan area

338,440 km²

18.1 inhabitants per km²

1,157 km

542 km

Capital: HELSINKI

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

Life expectancy:

78 years for men
84 years for women
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
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 1\textsuperscript{st} of January to 31\textsuperscript{st} December 1966

• NFBC 1986 included all mothers with expected date of delivery between 1\textsuperscript{st} of July 1985 to 30 June 1986
STUDY POPULATIONS

96 % of all births

MOTHERS: 12 068
CHILDREN: 12 231

NFBC 1966

99 % of all births

MOTHERS: 9 362
CHILDREN: 9 479

NFBC 1986
DATA COLLECTIONS

NFBC 1966
Northern Finland Birth Cohort 1966


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

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
Questionnaires for young men health and behavior
Questionnaires about health, behavior, work and social background, and clinical examination
Questionnaires about health, behavior, work and social background, and clinical examination

Employment, unemployment and pensions (Register of Finnish Centre for Pensions)
Hospitalizations and diagnoses (Hospital discharge register, inpatients/outpatients)
Medications and sick leaves (Social Insurance Institution of Finland, KELA)
Investments (EuroClear -register), earnings
Infectious diseases (Finnish register of infections)
Cancers (Finnish register of cancers)
Death and death causes (Finnish register of deaths)
Northern Finland Birth Cohort 1966:
Data collection at 45-46 years in 2012 - 2014

Health, behaviour, work and lifestyle
- Diet, FFQ
- Fitness/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

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

Study nurse:
• Thermal perception thresholds and tolerance
• Pressure pain threshold and tolerance
<table>
<thead>
<tr>
<th>Scale/Metric</th>
<th>31 y</th>
<th>46 y</th>
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</thead>
<tbody>
<tr>
<td>Anxiety &amp; Depression – SCL</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anxiety &amp; Depression – GHQ</td>
<td>X</td>
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<tr>
<td>Depression – BDI</td>
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<tr>
<td>Anxiety – GAD, STAI</td>
<td>X</td>
<td></td>
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<tr>
<td>Temperament – TCI</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Alexithymia – TAS</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Optimism – LOT</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Schizotypy – SAS, PER, PAS, HPS</td>
<td>X</td>
<td></td>
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</tbody>
</table>
Northern Finland Birth Cohort 1966

Birth
N=12231

31 year old followup
Clinical and questionnaire
N=5973

Only questionnaire
N=2717

Only clinical
N=34

No 31v data
N=3507

46 year followup
Clinical and questionnaire
N=5709

Only questionnaire
N=1378

Only clinical
N=118

No 46v data
N=5026
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
Northern Finland Birth Cohort 1986

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

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)

NFBC 1986 - psychiatric scales

<table>
<thead>
<tr>
<th>7-8 y</th>
<th>15-16 y</th>
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<tbody>
<tr>
<td>ADHD, Internalizing, Externalizing – Rutter B (parents)</td>
<td>X</td>
</tr>
<tr>
<td>ADHD, Internalizing, Externalizing – Rutter A* (teachers)</td>
<td>X</td>
</tr>
<tr>
<td>ADHD – SWAN (parents)</td>
<td>X</td>
</tr>
<tr>
<td>Internalizing, Externalizing – YSR (self-report)</td>
<td>X</td>
</tr>
<tr>
<td>Psychotic-like symptoms – PROD (self-report)</td>
<td>X</td>
</tr>
<tr>
<td>Alexithymia – TAS (self-report)</td>
<td>X</td>
</tr>
</tbody>
</table>

+ 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)

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:
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)


Cognition in psychiatric subsamples (NFBC 1986)

- psychosis risk study (22-24y), n=329

- 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

- 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...
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.

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%


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
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.

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.

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.


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.

Brain structural changes in women and men during midlife.


- 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.


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).

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 | b = -0.346 | BZDy |
| | p = 0.088 | p = 0.037 | b = -0.091 p = 0.176 |
| Total GM | b = -0.380 | b = -0.151 | CPZy |
| | p = 0.012 | p = 0.036 | b = -0.229 p = 0.283 |
| Cerebrum | b = -0.261 | b = -0.324 | BZDy |
| | p = 0.092 | p = 0.048 | b = -0.095 p = 0.702 |
| Cerebrum GM | b = -0.387 | b = -0.152 | CPZy |
| | p = 0.012 | p = 0.036 | b = -0.229 p = 0.283 |
| Lateral ventricles | b = -0.458 | b = 0.355 | CPZy |
| | p = 0.003 | p = 0.037 | b = -0.487 p = 0.035 |
| Caudate | b = -0.294 | b = -0.489 | BZDy |
| | p = 0.062 | p = 0.002 | b = -0.350 p = 0.141 |
| Putamen | b = -0.303 | b = -0.266 | n.s. |
| | p = 0.074 | p = 0.144 | |
| Thalamus | b = -0.344 | b = -0.360 | CPZy |
| | p = 0.030 | p = 0.033 | b = -0.153 p = 0.500 |
| Hippocampus | b = -0.340 | b = -0.184 | CPZy |
| | p = 0.040 | p = 0.306 | b = -0.245 p = 0.214 |
| | hospitalization days b = -0.788 p < 0.001 |
| Accumbens | b = -0.378 | b = -0.404 | CPZy |
| | p = 0.018 | p = 0.018 | 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.

YEARS FROM FIRST HOSPITAL ADMISSION TO DISABILITY PENSION

Adj. OR 6.5 (1.8-23.1)

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


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.

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.

MATERIAL REQUEST
NFBC 1966 AND 1986
Northern Finland Cohorts

Northern Finland Cohorts comprise collections of data and biological samples from large population studies that are administrated by the Northern Finland Birth Cohorts’ Project Center at the Medical Faculty, University of Oulu.

The Northern Finland Birth Cohorts, NFBC1966 and NFBC1986, form a longitudinal research program which aims to promote health and well-being of the population. The data has been collected from more than 20,000 individuals, who have been followed on a regular basis since antenatal period by health care records, questionnaires and clinical examinations as well as data on their parents and offspring (total n ~ 70,000). In addition cohorts from northern Finland aging individuals, Oulu50 and Oulu55, and a population study, The...
### Material Request

#### Title of the material request

**Short description of the material request**

<table>
<thead>
<tr>
<th>Researcher(s)</th>
<th>e-mail</th>
<th>Family name</th>
<th>First name</th>
<th>Employee</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="mailto:mema.mannikko@oulu.fi">mema.mannikko@oulu.fi</a></td>
<td>Mannikko</td>
<td>Mirka</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Unit/Department

- **Email:** mema.mannikko@oulu.fi
- **Family Name:** Mannikko
- **First Name:** Mirka
- **Employee:** Centre for Life Course Health Research
- **Contact Person:**

#### Dates

- **Material request submitted:** not stated yet
- **Material Request received:** not stated yet

#### Additional Information

- **Research Plan and List of Variables (including names of data consultants)**
- **Short title (max 10 characters)**
- **Keywords (4-6)**
- **Northern Finland Birth Cohorts' data:**
  - Cohort 1985
  - Cohort 1995
- **Type of request:**
  - Analysis
  - Additional variables
  - Publication
- **Original material request number**
- **Invoicing address**
- **VAT Number**
- **User policies**
- **Accepting NFBC User policies:**
  - I have read and informed the research group about the NFBC data user policies. I accept the terms and conditions regarding the user policies and take responsibility of the data usage on behalf of the research group.
  - Yes

---

https://www.greip.fi/secure/app.dll/request/details.zmi?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

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<tr>
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<th>2013</th>
<th>2014</th>
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<tr>
<td>Oulu University</td>
<td>55.0 %</td>
<td>60.4 %</td>
<td>70.2 %</td>
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<tr>
<td>Other domestic</td>
<td>14.6 %</td>
<td>18.5 %</td>
<td>10.4 %</td>
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<tr>
<td>International</td>
<td>30.3 %</td>
<td>21.0 %</td>
<td>19.5 %</td>
</tr>
</tbody>
</table>

- 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)
RESEARCH TEAMS AND COLLABORATORS

- Prof Jouko Miettunen
- Adj Prof Erika Jääskeläinen
- Prof Juha Veijola
- Prof Markku Timonen
- Prof Leena Ala-Mursula
- Peter Jones, Graham Murray, Golam Khandaker, Jennifer Barnett, John Suckling (University of Cambridge, UK)
- John McGrath (University of Queensland, Australia)
- Tomas Paus, Zdenka Pausova (University of Toronto, Canada)
- Alex Mason, Mary Chmelka, Jukka Savolainen (University of Michigan, USA)
- José Manjón (Polytechnic University of Valencia, Spain)
- Anthony Ahmed (Weill Cornell Medical College, NY, USA)
- Nelson Freimer, Susan Smalley (UCLA, USA)
- Brian Miller (Augusta University, USA)
- Alina Rodriguez (Imperial College London, UK)
- Sarah Whittle, Chris Pantelis (University of Melbourne, Australia)
THANK YOU AND WELCOME TO OULU!

CONTACT: jouko.miettunen@oulu.fi  www.oulu.fi/nfbc