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# Cohort profile: life with neurofibromatosis 1 – the Danish NF1 cohort

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## ABSTRACT

**Purpose** The Danish neurofibromatosis 1 (NF1) cohort was initiated to study health-related, socioeconomic and psychological consequences of living with the monogenetic disorder NF1 using a nationwide and population-based approach.

**Participants** The cohort includes all 2467 individuals in Denmark who were hospitalised with or due to NF1 from 1977 to 2013 or registered in the RAREDIS Database (1995–2013), a national clinical database for rare diseases, or both. A comparison cohort matched to individuals with NF1 on sex and date of birth was identified in the Civil Registration System (n=20 132).

**Findings to date** All cohort members were linked to the unique Danish registries to obtain information on hospital contacts, birth outcomes, education and partnership. A questionnaire was completed by 244 of the 629 adult cohort members with NF1 registered in the RAREDIS Database to evaluate the psychosocial and emotional burden. Further, neuropsychological tests were performed on 103 adult cohort members with NF1 and 38 adult population comparisons. To date, six studies have been published. Individuals with NF1 had an increased risk for (1) hospitalisation for disorders affecting all organ systems of the body throughout all decades of life, (2) psychiatric disorders, (3) attaining a short or medium long education and (4) not forming a life partner. Women with NF1 had an increased risk for spontaneous abortions and stillbirths. Finally, adults with NF1 had an impaired quality of life and a high need for professional support for physical, psychological and work-related problems, which was partly associated with disease severity and visibility.

**Future plans** The cohort will regularly be updated with newly diagnosed patients in the RAREDIS Database as well as with outcome information in the Danish registries. New studies are in progress to assess other medical and socioeconomic dimensions of living with NF1.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Danish neurofibromatosis 1 (NF1) cohort is a unique data source for investigating the consequences of living with NF1.
⇒ Despite being a rare disorder, the inclusion of all known individuals with NF1 in Denmark enables assessment of rare outcomes, new hypotheses and age-specific manifestations of NF.
⇒ The cohort combines registry data with information obtained in questionnaires and neurocognitive tests to give a comprehensive description of NF1.
⇒ Individuals with NF1 who have not been hospitalised or registered in the clinical database are not included in our cohort.
⇒ A comparison group is lacking in the questionnaire studies, and as Danish norm data are not available for all measures, we have to rely on international norm data.

## INTRODUCTION

The Danish neurofibromatosis 1 (NF1) cohort was initiated to investigate health-related, socioeconomic and psychological consequences of living with the single gene disorder NF1 using a nationwide and population-based approach. NF1 is one of the most common mendelian disorders, with an incidence of up to 1 in 2000 livebirths.[1] About 50% of the cases are inherited from a parent, whereas the other 50% are due to de novo *NF1* variants.[2]

NF1 is an unpredictable disorder that varies widely in severity and clinical manifestations. A hallmark feature of NF1 is neurofibromas, which are benign cutaneous lesions, subcutaneous tumours that grow from nerves or plexiform neurofibromas; the latter two of which carry a risk of malignant transformation.[3] Other clinical features include café-au-lait macules (pigmentary lesions of the skin), skeletal dysplasia, Lisch nodules (iris hamartomas) and optic pathway glioma.[4] The lifetime cancer risk for individuals with NF1 has been estimated to 60%[5] and is the main reason for the reduced life expectancy up to 16.5 years for men and 26.1 years for women with NF1.[1]

Although NF was formally described back in 1882 by Friedrich Daniel von Recklinghausen,[6] knowledge about all features of NF1, especially in adults, is still sparse. A wide range of medical, cognitive, social and behavioural problems have been associated

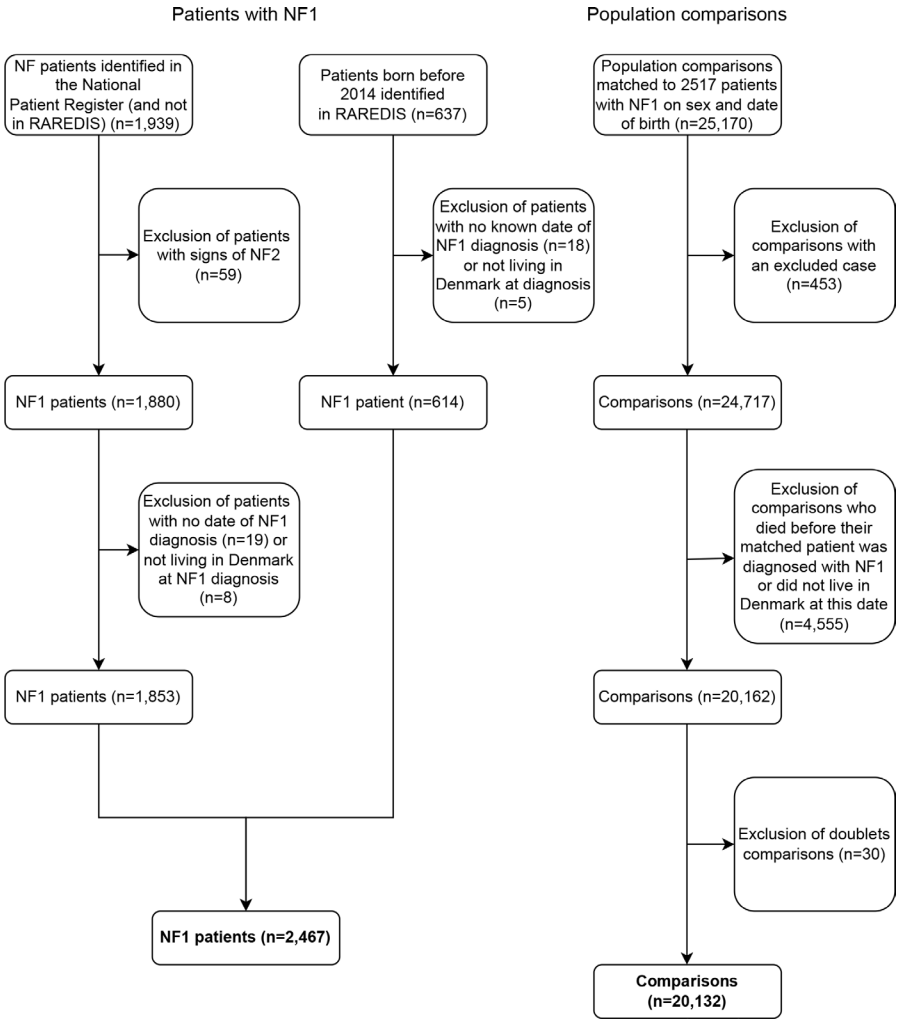


**Figure 1** Flow chart of cohort members in register-based studies.

with NF1.[2] However, most previous research was based on small populations, relied on self-reported outcomes or lacked a population-based approach. Thus, we initiated the Danish NF1 cohort to permit a comprehensive assessment of the multifaceted burden of living with NF1 by combining information from national registries, a clinical database, questionnaires and neuropsychological tests. As NF1 is a rare disorder, few countries are capable of initiating a large, national cohort of individuals with NF1. The use of a population-based cohort to assess the consequences of living with NF1 reduces the risk of a selective inclusion and dropout, and limits the risk of reporting bias, for example, from case series at academic medical centres. Finally, we were able to establish a comparison cohort randomly sampled from the Danish general population.

To depict life with NF1, the aim of establishing this comprehensive NF1 cohort was to assess the somatic and psychiatric disease burden in individuals with NF1 as well as to assess how they manage the transition from childhood into adolescence and adulthood by determining the following psychosocial and socioeconomic achievements or life goals: cohabitation, leaving home and educational attainment. Finally, the aim was to pilot investigation of the psychosocial burden and neurocognitive function among adults with NF1 using questionnaire data and neurocognitive tests.

## COHORT DESCRIPTION

Denmark offers exceptional opportunities for carrying out population-based research because of its civil registration system based on unique personal identification numbers given to all inhabitants on 2 April 1968 and since then at birth and the existence of a number of unique population-based, nationwide administrative registries with information on for example medical and surgical hospitalisation and educational attainment. Denmark has a tax-funded welfare system, which supplies education, social welfare and healthcare free of charge. This system, in combination with the tradition for administrative registration of both health and socioeconomic factors with strong legislation to protect the individual, enables the use of grouped data for research and forms a unique platform to perform studies that have never before been conducted on a nationwide basis.

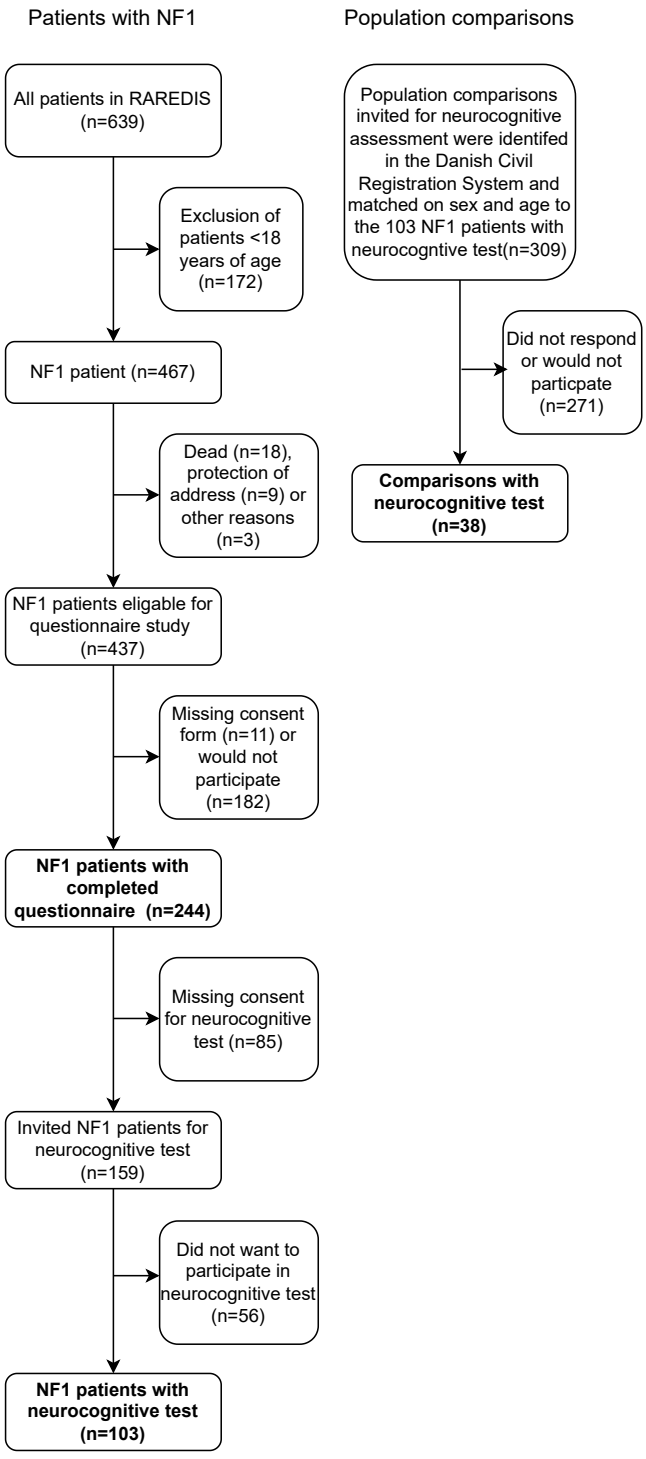


**Figure 2** Flow chart of study participants in questionnaire study and neurocognitive tests.

Table 1 Register-based outcome measures and sources in the NF1 cohort

| Main outcome | Subcategories | Data source | Availability in the danish NF1 cohort |
|---|---|---|---|
| Somatic disease burden | Hospitalisations in 12 main diagnostic groups and 146 specific diagnoses and subgroups based on ICD | Danish National Patient Registry[7] | 1977–2016. Outpatient and emergency contacts since 1995. |
| Psychiatric disease burden | Hospital contacts for psychiatric disorders grouped in 13 diagnostic groups | The Danish Psychiatric Central Research Register[13] | 1969–2016. Outpatient and emergency contacts since 1995. |
| Pregnancy | Pregnancies, abortions, livebirths and stillbirths | The Danish Medical Birth Register[14]<br>Register on Induced Abortions[15]<br>The Danish National Patient Registry[7] | 1973–2016; 1977–1994; 1977–2016. |
| Cohabitation | Forming and ending marital and cohabitation relationships | Household and Family Statistics, a national database provided by Statistics Denmark[16] | 1980–2015 |
| Leaving home | Living at an address which is not a care centre and is different from that of both parents | The Danish Civil Registration System[12] and The Central Register of Buildings and Dwellings[17] | 1980–2015 |
| Educational delay and attainment | Highest attained education at age 30 years and delays in educational achievements | The Danish Education Registry[18] | 1981–2015 |

ICD, International Classification of Diseases; NF1, neurofibromatosis 1.

## Study population

The NF1 cohort was established by combining data from the national Danish Patient Registry with data from a database for rare diseases (RAREDIS). Initially, we included all 2576 individuals, alive or born after 2 April 1968, who have been hospitalised with or for NF according to the International Classification of Diseases version 8 (ICD-8) 743.49 or ICD-10 Q85.0 since the establishment of the Patient Registry in 1977 and until 31 December 2013 (see flow chart, figure 1). The Patient Registry is a population-based administrative registry and includes information on all somatic inpatient hospitalisations; psychiatric hospitalisation and outpatient and emergency visits were added to the registry in 1995.[7] The ICD system, however, does not differentiate between NF1 and the even rarer NF2, which is clinically and genetically distinct from NF1.[8] Thus, we excluded 59 individuals from the cohort, who had a tumour or tumour combinations or a discharge history

Table 2 Outcome measures and sources for questionnaire study

| Main outcome | Subcategories | Data source |
|---|---|---|
| Standardised measures | | |
| Quality of life | Physical, emotional, social and cognitive functioning, communication, worry, perceived physical appearance, pain and hurt, paraesthesia (sensory disturbance), skin irritation, sensation, movement and balance, daily activities, fatigue, anxiety about treatment and sexual functioning | The Paediatric Quality of Life Inventory developed for adults with NF1[38] |
| Depression | Nine symptoms, including level of interest in doing things, feeling down or depressed, difficulty in sleeping, low energy level, poor eating habits, poor self-perception, poor ability to concentrate, low speed of functioning and thoughts of suicide | The standardised Patient Health Questionnaire depression scale-9 applying the nine criteria for the DSM-IV depression diagnosis[39] |
| Anxiety | Seven core symptoms of anxiety, including feeling nervous, not controlling worrying, worrying too much, trouble in relaxing, being restless, being irritable and feeling afraid | Seven-item Generalised Anxiety Disorder scale[40] |
| ADHD traits | A symptom checklist of 18 criteria related to inattention and hyperactivity/impulsivity | Adult ADHD Self-Report Scale II[41] |
| Fatigue | Only the subscales of reduced activity, mental fatigue and physical fatigue were included | The self-reported questionnaire: Multidimensional Fatigue Inventory-20[42] |
| Self-developed measures | | |
| Disease severity | 13 items related to NF1, including cutaneous and plexiform neurofibromas, malignant tumours and the effect of current treatment | We developed a self-report version of the Riccardi scale to group disease severity into ‘mild’, ‘moderate’ or ‘severe’[43] |
| Disease visibility | Six items related to the visibility of NF1 when fully dressed considering café-au lait spots, tumours on neck or face or noticeable limp | We developed a self-report version of the Ablon scale into three groups (‘mild’, ‘moderate’ and ‘severe’)[44] |
| Need for support | Problems within the following domains: physical-related, psychological-related, sexual-related, family-related, work-related and economic problems | We developed our own six-item scale rating from ‘never’ to ‘a high extent’ |

ADHD, Attention Deficit Hyperactivity Disorders; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; NF1, neurofibromatosis 1.

Table 3 Outcome measures and sources for neurocognitive study

| Main outcome | Subcategories | Data source |
|---|---|---|
| Intelligence | Vocabulary (word knowledge and the ability to express definitions of words verbally), Similarities (language conceptualisation, verbal abstraction and analogical verbal reasoning), block design (spatial perception and problem solving) and Matrix Reasoning (non-verbal abstract problem-solving, inductive reasoning and spatial reasoning ability) | An abbreviated version of the Wechsler Adult Intelligence Scale Fourth Edition[45] |
| Other cognitive functions | Attentional set-shifting, planning and planning time, working memory, visual short-term memory, sustained attention and movement time and reaction time as well as visuospatial constructional ability and visuospatial memory | Selected tests from the computerised neuropsychological test battery from the Cambridge Neuropsychological Test Automated Battery (Connect, Tablet version), including Multitasking Test, One-touch Stocking of Cambridge, Spatial Working Memory, Spatial Span, Rapid Visual Information Processing, Reaction Time and Rey's Complex Figure Task[46] |
| Autism spectrum disorder traits | Deficits in social responsiveness | The self-rating Social Responsiveness Scale-Second Edition[47] |
| Executive functions | Inhibit, shift, emotional control, self-monitor, initiate, working memory, plan/ organise, task monitor and organisation of materials | The self-reported Behaviour Rating Inventory of Executive Function-Adult Version[48] |

in the Patient Registry compatible with NF2.[9] We supplemented the NF1 cohort with individuals registered with NF1 in the RAREDIS Database.[10] The database includes information on patients who were followed in one of two national centres for rare diseases between 1995 and 2013 located at Aarhus University Hospital and Copenhagen University Hospital, Rigshospitalet. All diagnoses are confirmed using the diagnostic criteria set up by the National Institute of Health, USA[11] or by molecular genetic testing. All inhabitants in Denmark with known NF1 are encouraged to be followed regularly in one of the two centres free-of-charge irrespective of NF1 disease severity.

Table 4 Characteristics of the NF1 cohort and comparison cohort

| Characteristic | NF1 cohort (n=2467) | Comparison cohort (n=20 132) |
|---|---|---|
| Sex (%) | | |
| Women | 1241 (50) | 10 140 (50) |
| Men | 1226 (50) | 9992 (50) |
| Birth year (%) | | |
| 1890–1910 | 66 (3) | 442 (2) |
| 1911–1930 | 222 (9) | 1720 (9) |
| 1931–1950 | 466 (19) | 4016 (20) |
| 1951–1970 | 576 (23) | 4756 (24) |
| 1971–1990 | 574 (23) | 4148 (21) |
| 1991–2013 | 563 (23) | 5050 (25) |
| Mean age at entry (SD) | 29.8 (23.4) | 29.3 (23) |
| Death during follow-up | 727 (29) | 3337 (17) |
| First hospitalisation* (%) | | |
| Any | 1716 (70) | 10 004 (50) |
| Digestive systems | 497 (20) | 2953 (15) |
| Cancer | 457 (19) | 1893 (9) |
| Respiratory system | 454 (18) | 2501 (12) |
| Circulatory system | 452 (18) | 3153 (16) |
| Nervous system | 403 (16) | 1304 (7) |

*Any first hospitalisation and hospitalisations in the five most common main diagnostic groups (based on ICD-8 and ICD-10) for individuals with NF1.
ICD, International Classification of Diseases; NF1, neurofibromatosis 1.

Each member of the NF1 cohort was matched on sex and date of birth to up to 10 population comparisons randomly selected from the Danish Civil Registration System[12] to represent the Danish background population. All individuals in the comparison cohort had to be alive on 2 April 1968 or be born thereafter and without a registration of a NF1 diagnosis in the Patient Registry or in the RAREDIS Database on the date their matched patient was diagnosed with NF1 (n=25 170).

All cohort members were linked to the Danish Civil Registration System to obtain information on vital status and migration. We excluded individuals with no known date of NF1 diagnosis (n=37) (figure 1). We also excluded cohort members who did not live in Denmark at diagnosis, comparisons with an excluded matched case, those who died before or did not live in Denmark when their matched patient was diagnosed with NF1 as well as doublet comparisons, leaving 20 132 individuals in the comparison cohort.

### Participants in questionnaire study

Of the 639 individuals registered in the RAREDIS Database with NF1 in the period 1977–2016, 467 were adults aged ≥18 years living in Denmark (see flow chart, figure 2). We excluded 30 adults due to death, protection of address or other reasons, leaving 437 adults with NF1 eligible for participation. The 437 adults were mailed an invitation letter and a paper-based questionnaire, and 244 adults consented to participate and completed the questionnaire (response rate=56%).

### Participants in neurocognitive tests

Finally, 159 of the 244 participants in the questionnaire study gave written consent to be invited for neurocognitive

Table 5 Baseline characteristics of participants in questionnaire study and neurocognitive tests

| Characteristic | NF1 cohort questionnaire study (n=244) | NF1 cohort neurocognitive study (n=103) | NF1-free comparisons neurocognitive study (n=38) | P value* |
|---|---|---|---|---|
| Sex (%) | | | | 0.614 |
| Women | 151 (62) | 51 (50) | 17 (45) | |
| Men | 93 (38) | 52 (50) | 21 (55) | |
| Age, mean (SD, years) | 40.2 (14.7) | 43.2 (15.9) | 45.3 (17.3) | 0.516 |
| Highest attained education (%) | | | | NA† |
| Short | 43 (18) | 15 (15) | <5‡ | |
| Medium | 84 (34) | 41 (40) | <15‡ | |
| Long | 84 (34) | 35 (34) | 23 (61) | |
| Missing | 33 (14) | 12 (12) | 0 (0) | |
| Employment status (%) | | | | NA† |
| Employed | 100 (41) | 14 (14) | 27 (71) | |
| Unemployed | 37 (15) | 44 (43) | <5‡ | |
| Social transfer payments§ | 76 (31) | 30 (29) | <5‡ | |
| Pension | N/A | 11 (11) | 6 (16) | |
| Missing information | 7 (3) | 4 (4) | 0 (0) | |
| Accommodation (%) | | | | <0.0001 |
| Living alone | 88 (36) | 46 (45) | 6 (16) | |
| Living together with spouse | 117 (48) | 43 (42) | 28 (74) | |
| Living together with parent | 22 (9) | 9 (9) | 0 (0) | |
| Living in a shared home | 8 (3) | 0 (0) | 4 (11) | |
| Living in an institution | <5 | 0 (0) | 0 (0) | |
| Missing | <10 | 5 (5) | 0 (0) | |
| Cohabitation status (%) | | | | 0.001 |
| Having a partner | 133 (55) | 49 (48) | 31 (82) | |
| Having no partner | 107 (44) | 51 (50) | 7 (18) | |
| Missing | 4 (2) | 3 (3) | 0 (0) | |

*Independent-samples t-tests and $\chi^2$ analyses were conducted for normally distributed data and nominal data.
†P value could not be calculated due to low number of participants in some of the categories.
‡Due to reporting restrictions, the exact number is not shown.
§Employed individuals with wage subsidies, disablement rehabilitation, sick leave, or early pension.
NA, not availale; NF1, neurofibromatosis 1.

testing (see flow chart, figure 2). In total, 103 consented to participate (response rate=65%) and were tested either in their own home or at a local centre of the Danish Cancer Society by psychology students trained by a skilled psychologist and senior researcher from Copenhagen University Hospital, Mental Health Services Copenhagen. A total of 309 NF1-free individuals sampled from the Danish Civil Registration System matched on sex and birth year were invited as a comparison group. All potential comparisons were contacted by mail and 38 consented to participate (response rate=12%) and provided data on neurocognitive tests.

### Patient and public involvement

Seven patients with NF1 were consulted during the initial phase of setting up the cohort. We recruited patients from the two national Centres for Rare Diseases and the Danish Association for NF. The patients participated in interviews and a focus group session to discuss relevant research questions for the questionnaire study and neurocognitive assessments. The early input from patients were included in the final questionnaire and the neurocognitive assessments. The current results of the research programme based on the NF1 cohort have been disseminated to the Danish public by providing summaries of the results in newsletters sent by the Danish Cancer Society and published online on www.cancer.dk. Finally, we have presented all published results to members of the Danish Association for NF at their annual meeting on 10 May 2021.

## MAIN OUTCOMES AND SOURCES

### Register-based outcomes

All cohort members were linked to several national registries to obtain individual-level information on health and sociodemographic data, including hospital history (The

Table 6 Main findings and implications of published studies within the Danish research programme 'life with NF1'

| Study | Participants | Findings | Impact |
|---|---|---|---|
| Data from registries | | | |
| Multisystem burden of neurofibroma tosis 1 | 2467 individuals with NF1 and 20 132 population comparisons | Individuals with NF1 have frequent clinical problems that persist and accumulate throughout life and require longer and more frequent hospitalisations. | As the consequences of somatic disease can influence school performance, education, employment as well as quality of life, lifelong follow-up in specialised NF1 clinics with the experts to address the pleiotropic manifestations of the disease is important. Additional research is needed focusing on targeted interventions to include patient counselling, optimal follow-up and support that address the findings outlined in this comprehensive study. |
| Psychiatric disorders | 905 individuals with NF1 and 7614 population comparisons | Individuals with NF1 are at increased risk for psychiatric morbidity. | Screening in this population might be important for early diagnosis and facilitation of appropriate and effective treatment to enhance the well-being for individuals with NF1. |
| Pregnancy outcomes in women | 1006 women with NF1 and 10 020 female population comparisons | Women with NF1 have the same probability of pregnancies as women in the background population, but a higher risk for stillbirths and spontaneous abortions. | Considering this higher risk of adverse pregnancy outcomes, women with NF1 need close monitoring already in the beginning of their pregnancy. |
| Forming and ending marital or cohabitation relationships | 787 individuals with NF1 and 7787 population comparisons | Individuals with NF1 are less likely to engage in an intimate relationship than NF1-free individuals and are older when they form their first relationship. | Our findings emphasise the hardship and struggles of this lifelong condition; not only in terms of the somatic consequences and complications of NF1 but also the social consequences of the condition which may have a potentially huge impact on daily life. |
| Educational delay and attainment | 550 individuals with NF1 and 4295 population comparisons | A lower educational level is seen in individuals with NF1 and they are older when graduating mandatory school. | NF1 is associated with cognitive deficits and developmental disorders, which can affect academic skills, educational level and type of job. Thus, focus on vulnerable children with NF1 in school is important for optimal learning assistance and counselling. |
| Data from questionnaires | | | |
| Quality of life | 244 individuals with NF1 | Adults with NF1 experience a lower quality of life and psychosocial well-being and a higher need for support in daily life. | As NF1 affects daily life, follow-up care and individual counselling and support are needed in adults with NF1, especially among those severely affected by their disease. |

NF1, neurofibromatosis 1.

Danish National Patient Registry[7]), psychiatric hospital contacts (The Danish Psychiatric Central Research Register[13]), pregnancy outcomes (The Danish Medical Birth Register,[14] Register on Induced Abortions[15] and The Danish National Patient Registry[7]), marriage and cohabitation (Household and Family Statistics, a national database provided by Statistics Denmark[16]), leaving home (The Danish Civil Registration System[12] and The Central Register of Buildings and Dwellings[17]) and education (The Danish Education Registry[18]). A description of the main outcome measures and their sources is seen in table 1.

### Questionnaire outcomes

The outcome measures in the questionnaires included: quality of life (QoL), severity of ADHD symptoms, symptoms of depression and anxiety, fatigue, disease severity, disease visibility and need for and received support. We used both standardised measures as well as self-developed measures, which are described in table 2.

### Neurocognitive outcomes

Finally, we assessed the neurocognitive functioning by measuring: intelligence, other cognitive functions across several domains and executive functions. We also assessed

autism spectrum disorder traits. The specific tests and questionnaire and their measurements are presented in table 3.

### Statistical analysis

Different statistical models have been used to assess the association between the selected exposures and NF1 in the published studies. In the register-based studies, relative risk estimates were calculated using survival analysis for time-to-event data (studies of multisystem burden, psychiatric disorders, pregnancy outcomes and relationships) and multinomial logistic regression (study of education). We also estimated proportion ratios (study of pregnancy outcomes) as well as cumulative incidences and mean cumulative number of hospital contacts (studies of multisystem burden and psychiatric disorders) or pregnancies (study of pregnancy outcomes). In the questionnaire-based study, both normal linear models and logistic regression models were used to examine the associations between the different exposures and QoL.

## FINDINGS TO DATE

### Characteristics of participants

Table 4 shows the characteristics of the large NF1 cohort of 2467 individuals with NF1 and the comparison cohort of 20 132 individuals. The distribution of men and women was equal in the cohort, with the oldest cohort members born in 1890. The mean age at study entry was 29.8 years. During follow-up through 31 December 2016, 30% (n=727) of the NF1 cohort members died, almost twice as many as in the comparison cohort (17%, n=3337).

Baseline characteristics of the participants in the questionnaire study and neurocognitive tests are presented in table 5, where it is shown that the adults with NF1 are different than the NF1-free comparisons on several characteristics, including education, employment and cohabitation status.

### Somatic and psychiatric disease burden

Currently, six studies based on this NF1 cohort have been published.[9 19–23] We have given a comprehensive description of the overall somatic disease burden in individuals with NF1. Using information from the Danish Patient Registry, we found that that the risk for a first hospitalisation for any somatic disorder was twice as high in individuals with NF1 as for the comparison group. Furthermore, individuals with NF1 had more hospitalisations and spent more days in hospital than the population comparisons. The increased risks were observed for both children and adults with NF1. Individuals with NF1 had an increased absolute risk for a hospitalisation in all main diagnostic groups, highest for disorders of the nervous system, benign and malignant neoplasms, and disorders of the digestive and respiratory systems.[9] We have also shown that the risk for psychiatric hospitals contacts, including developmental disorders like attention deficit/hyperactivity disorders, autism spectrum disorders and intellectual disabilities, were increased in children with NF1. Only females with NF1 continued to face an increased risk for psychiatric hospitals contact in early adulthood.[19]

### Pregnancy outcomes

The probability of a pregnancy, live birth, stillbirth and abortion was assessed in 1006 women with NF1 in the fertile age (15–49 years). The cumulative incidence of a first pregnancy was only slightly lower in women with NF1 (74%; 95% CI 70% to 77%) at age 50 years than in women in the comparison group (78%; 95% CI 77% to 79%). The HR of a pregnancy was similar in women with and without NF1 after adjustment for somatic and psychiatric disease, which indicates that the probability of becoming pregnant is similar for women with and without NF1. However, women with NF1 had an increased risk for spontaneous abortions and stillbirths.[20]

### Educational achievements and cohabitation

Two studies of educational achievements and cohabitation using national registries for outcome identification have been published.[21 23] The OR for obtaining a short and medium-long education compared with a long education was three fold (95% CI 2.55 to 3.99) and 1.29 fold (95% CI 0.99 to 1.69) higher, respectively, for individuals with NF1 vs population comparisons after adjusting for birth year, sex, psychiatric and somatic morbidity, and maternal education. Furthermore, individuals with NF1 graduated mandatory school significantly later.[21] As for cohabitation, individuals with NF1 were less likely to form a relationship (either by marriage or cohabitation) (HR 0.65; 95% CI 0.58 to 0.73) than individuals in the comparison group. However, once the relationship was established, couples with a NF1-individual were not at greater risk of ending the relationship.[23]

### Quality of life

Using patient-reported outcomes, we observed an impaired QoL in adults with NF1 (mean=81.3, 95% CI 76.2 to 86.4). In addition, 19% of the adults with NF1 reported symptoms of depression (mean=5.7; SD=5.4) and 15% reported anxiety (mean=5.1; SD=5.2) at a clinical level. Adults with NF1 also reported a high requirement for professional support for physical, psychological and work-related problems. We found that disease severity and partial visibility were negatively associated with psychosocial well-being and a requirement for support.[22]

## FUTURE PLANS

The NFI cohort will generate state-of-the art knowledge on the pleiotropic consequences of *NF1*, the underlying determinant, including somatic, psychiatric, psychological, socioeconomic and neurocognitive consequences. We are currently updating our NF1 cohort and the comparison group to include patients diagnosed after 2013. We will also continue our research and the projects will focus on both clinical (including cancer risk) and

socioeconomic consequences of NF1 (including school grades, employment status, occupational position and income) and predictors of health-related QoL. A future goal is to genotype individuals with NF1 to identify any genotype–phenotype correlations and familial aggregations of certain features to increase the understanding of NF1.

## DISCUSSION

We established the Danish NF1 cohort in 2014 to provide a comprehensive assessment of the multifaceted burden of living with NF1 in Denmark, which had not previously been done. Currently, six studies based on this NF1 cohort have been published. We have shown that individuals with NF1 have an increased risk for somatic disorders affecting all organ systems and that the increased risk persists throughout life. We also found an increased risk for psychiatric hospital contacts, especially in childhood and adolescence. Previous studies focused on the risk for single diseases (eg, cancer[5]), disease groups (eg, neurological conditions[24] or cerebrovascular disease[25]) or reported only prevalence when assessing psychiatric comorbidity.[26 27]

We found that the probability of becoming pregnant was similar for women with and without NF1, but that women with NF1 had an increased risk of spontaneous abortions and stillbirths. Other studies have observed an increased risk for pregnancy complications in women with NF1,[28 29] but have not investigated the pregnancy outcomes. We have also reported a lower educational level in individuals with NF1, which has later been confirmed in a population-based Finnish cohort study.[30] Our finding that individuals with NF1 were less likely to form a marital or cohabiting relationship contributes with knowledge on the social challenges that individuals with NF1 may face, including loneliness[31] and social dysfunction.[32] Finally, we were able to include cohort members for our questionnaire study and neurocognitive tests using a population-based design. Only the results based on the questionnaire data have been published. We found that adults with NF1 had an impaired QoL and a high need for professional support for both physical, psychological and work-related problems. Disease severity and partly visibility were associated with the psychosocial well-being and the requirement for support. An impaired QoL among adults with NF1 has also been reported in other studies[33] as well as the association between disease severity and QoL or skin-specific QoL.[34 35] As disease severity and to some degree visibility seem to be associated with QoL, the burden of psychological symptoms and special needs of support, screening for these characteristics might be useful to identify the most vulnerable individuals with NF1.

The main strength of the Danish NF1 cohort is the nationwide and population-based design using registries for identification of individuals with NF1 supplemented with patients from the clinical national RAREDIS Database. Due to a tax-financed health system in Denmark, all inhabitants with NF1 are offered treatment in a hospital and follow-up in a national centre for rare disease free-of-charge. Furthermore, we used the registries to randomly select a comparison group of individuals free of NF1 at entry. The registries in Denmark have virtual complete registration,[36] including information on immigration, which reduces losses to follow-up. The participants in the questionnaire and neurocognitive study were sampled among individuals registered in the RAREDIS Database, which also ensured a population-based design in these studies. Furthermore, the nationwide registries provided an unselected data source with unique information on different health and socioeconomic outcomes. For the register-based studies, we did not have to rely on self-reported outcomes, which is a main strength, as we were able to depict a complete hospital history for each cohort member.

The cohort also has some limitations. As we only included individuals with NF1, who had been hospitalised with or for their NF1 or registered in the RAREDIS Database, some individuals with NF1 probably less affected by their NF1 disease may not be included in our cohort as well as some individuals who only had features of NF1 but in fact proved to have other disorders. In addition, the Danish National Patient Registry was established in 1977; thus among those individuals born before this year, a potential gap of hospitalisations exists between birth and start of the register. However, this gap applies to both individuals with NF1 and the comparisons. Despite the use of a population-based approach to identify adults with NF1 for the questionnaire and neurocognitive study, only 244 and 103 adults participated, respectively, which limited the statistical power in these studies. Finally, we did not include a comparison group in the questionnaire study. Since Danish normative data are missing for some of the measures, we include international normative data, which might differ from data generated from a Danish background population.

Our overall goal of this cohort is to fill in knowledge gaps with population-based research on health-related and psychosocial aspects of NF1. Using a novel approach to study important aspects of this genetic disorder, we will add knowledge of the implications this complicated disease may have on life. The clinical information provided by these large nationwide studies is highly requested by the patients and their families as well as by the clinicians advising these patients. Experts recommend lifelong follow-up for NF1 patients with multiple healthcare providers using a multidisciplinary approach.[37] The results of the completed studies of health conditions and social aspects of life in this patient group in combination with potential predictors of well-being and functioning from the questionnaire studies can be used to develop a systematic plan for longitudinal screening and evidence-based guidelines for surveillance. The ultimate goals are to contribute to the development of targeted intervention strategies to improve the basis for patient counselling and to optimise follow-up procedures, leading to high quality

of care and sufficient support to NF1 patients (see also table 6).

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**Collaborators** The study group at the Danish Cancer Society Research Center, Childhood Cancer Research Group (Jeanette F Winther and Line Kenborg) welcomes collaborations based on data from the NF1 cohort. All data are stored on Statistics Denmark. Access to the established NF1 cohort is available through Statistics Denmark and requires application to the study group (including study protocols and collaborative agreements) as well as to Statistics Denmark.

**Contributors** KD and LK wrote the first draft of the manuscript. JJM and JFW designed and established the register-based NF1 cohort, while HH, JRØ and CE contributed to enrolling of patients in the two centres for rare diseases. PEB, KD and JRMJ contributed to patient enrolment in the questionnaire and neurocognitive studies. AK, MAD and LK collected data on the platform of Statistics Denmark and AK was responsible for data management. KD, HH, JRØ, PEB, SOD, MMH, CE, JJM, JFW and LK obtained funding to establish the NF1 cohort and continue the NF1 research using this cohort. All authors reviewed, critically revised and approved the manuscript. LK is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

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**Ethics approval** This study involves human participants and was approved by Danish Cancer Society: ID IORG0001095The Research Board of the Department of Defense US Army: under Award No. W81XWH-14-1-0054The Danish Health Data Authority: ID FSEID 00002527Danish Cancer Society Research Centers archive: 2018-DCRC-0012. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available on reasonable request. All data are stored on a secure platform at Statistics Denmark and can only be accessed remotely. The study group welcomes collaboration with other researchers. Study protocols can be planned in collaboration with us, and the data can be analysed accordingly at the server of Statistics Denmark. Access to data can only be made available for researchers who fulfil Danish legal requirements for access to personal sensitive data. Please contact JFW (jeanette@cancer.dk) or senior researcher LK (kenborg@cancer.dk) for further information.



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