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Running head: NF1 HEALTH SURVEY

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Health survey of adults with Neurofibromatosis 1 compared to population study controls

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Abstract

Neurofibromatosis type 1 (NF1) is a genetic, autosomal dominant multi-organ disease characterized by susceptibility to tumor formation, changes in skin pigmentation, skeletal abnormalities, and neuropsychological deficits. Clinical studies have shown impaired health-related quality of life (HQoL) in adults with NF1. However, little is known about HQoL in non-clinical NF1 samples. We conducted a cross-sectional self-report survey of 142 persons with NF1 (M age = 50.3 years, SD = 12.0, $range$ 32 to 80; 62.0% females) recruited from non-clinical settings. Several HQoL domains, including life satisfaction, mental health, sleep, pain, gastrointestinal problems, oral health, and social support were compared between the NF1 sample and 46,293 controls from the HUNT3 population study. We also examined gender differences within the NF1 sample and predictors of HQoL. Compared to controls, the NF1 sample reported significantly poorer life satisfaction, mental health, sleep, and oral health, and more pain, gastrointestinal problems, comorbid diseases, and memory problems. Several HQoL domains were significantly correlated. Mental health was the only unique significant predictor of overall life satisfaction. Women with NF1 reported significantly more mental health, sleep, and pain problems than men with NF1. Mental health assessment and management should be integrated into clinical care of persons with NF1 to potentially improve their HQoL.

Key words: Neurofibromatosis, NF1, quality of life, mental health

Health survey of adults with Neurofibromatosis 1 compared to population study controls

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by mutations or deletions of the neurofibromin gene of chromosome 17q11.2 (Abramowicz & Gos, 2014). NF1 is a multi-organ disease characterized by susceptibility to tumor formation, changes in skin pigmentation, skeletal abnormalities and neurological deficits, with an incidence of 1:2500/3000 (Williams et al., 2009).

Health-related quality of life (HQoL) represents an important outcome in disorders with no cure or specific treatment, such as NF1 (Birch & Friedman, 2012). A handful of cross-sectional self-report studies have examined how NF1 affects HQoL compared to norms or controls. Three studies assessed HQoL in NF1-patients with the Health Survey Short Form (SF-36), which covers physical function, limitations because of physical and emotional problems, social function, mental health, energy, pain, and health perception. Between them, these studies included 433 NF1-patients, and reported significantly lower scores on all domains of the SF-36 for NF1-patients compared to norms (Kodra et al., 2009; Page et al., 2006; Wolkenstein, Zeller, Revuz, Ecrosse, & Leplège, 2001). A few studies also considered more specific aspects of HQoL in adults with NF1. For example, two of the above-cited studies also measured skin-related quality of life and both found this measure to be predicted by increased perception of disease visibility (Kodra et al., 2009; Page et al., 2006). Another study found self-reported body image (i.e., insecurity/attractiveness) was poorer among 228 persons with NF1 compared to norm data and psoriasis patients (Granström, Langenbruch, Augustin, & Mautner, 2012). Finally, voice-related quality of life was poorer in a study of 29 persons with NF1 compared to study controls (Cosyns, Mortier, Janssens, & Van Borsel, 2012).

Two uncontrolled studies used HQoL measures developed specifically for the NF1 population. In a recent study of 50 NF1-patients, at least moderate problems regarding role and outlook on life, depression and anxiety, pain intensity, learning problems and sleeping, cosmetic appearance, vision, pain quality, behavior, and personality were reported by 10 to 42% of participants (Ferner et al., 2017). In a study of 134 persons with NF1, researchers administered a NF1-specific HQoL measure developed through literature and expert reviews and qualitative and cognitive data from persons with NF1 (Nutakki et al., 2013). Self-reported health was negatively associated with physical, emotional, social, and cognitive functioning, communication, worry, perceived physical appearance, pain, paresthesia, skin irritation, and fatigue.

Together, these studies have provided valuable insights into the complexity HQoL problems experienced by persons with NF1. However, there are still knowledge gaps. First, apart from seemingly strong evidence that disease visibility and gender do not predict general HQoL and that disease visibility and NF1 severity predict skin-related quality of life, there is lack of knowledge regarding predictors of HQoL for persons with NF1 (Vranceanu, Merker, Park, & Plotkin, 2013). Such knowledge is essential to practitioners, in order to prioritize areas to target to improve HQoL in NF1-patients.

Second, sample representativeness in earlier studies is questionable. With a few exceptions (Granström et al., 2012; Page et al., 2006), studies have mainly been based on clinic-recruited patients. One-quarter (25.9%) of the participants in Granström et al. (2012) and an unspecified number of participants in Page et al. (2006) were also recruited from specialist NF clinics. Although NF1 typically requires medical care, recruitment bias cannot be ruled out, as persons with NF1 with less clinical involvement may experience fewer HQoL-problems. Studies examining HQoL in non-clinical NF1 samples are therefore needed.

1 Third, little is known about gender differences within the NF1-population. As there
2 are considerable gender differences in health in the general population (e.g., more pain and
3 sleep problems among women, and less help-seeking behavior among men) (e.g., Nelson,
4 2014; Michelson et al., 2000; Mong & Cusmano, 2016), important gender differences in
5 HQoL may exist within the NF1-population. Such potential differences are important to
6 uncover, as they have implications for how practitioners tailor assessment of and
7 interventions for NF1-patients.
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10 Finally, previous studies have included patients from a wide age range, with a mean
11 age across studies around 40 years. More knowledge about HQoL in older persons with NF1
12 is needed. This is because older age in persons with NF1 has been associated with lower
13 scores in multiple domains of HQoL, including poorer physical function, vitality, general and
14 mental health, and skin-disease-related quality of life, as well as more social problems and
15 increased visibility of NF1 (e.g., Kodra et al., 2009; Page et al., 2006; Wolkenstein et al.,
16 2001). Other studies have not found age to predict HQoL, and according to a review, the
17 predictive role of age in NF1 is unclear (Vranceanu et al., 2013).
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20 **Purpose of the study**

21 The current study is a cross-sectional self-report survey of 142 persons with NF1 aged
22 30 years and older recruited from non-clinical settings. We surveyed multiple HQoL domains
23 and compared data to a large sample of 46,293 population controls. Our primary research
24 question is to examine the extent of HQoL problems among adults with NF1, who we expect
25 will have more problems than controls. Second, we examine gender differences within the
26 NF1-sample. Based on data from the general population, we expect that women with NF1
27 experience more pain and sleep problems than men with NF1, with no a priori expectations
28 on other domains due to limited or contradictory previous findings. Third, we examine
29 relations between HQoL domains within the NF1 sample, and aim to identify specific
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predictors of overall life satisfaction. We expect most HQoL domains will be correlated, with no a priori expectation of specific predictors, due to limited or contradictory findings from previous studies (Vranceanu et al., 2013).

Methods

Participants and procedures

The NF1 sample comprised 142 persons with NF1 (M age = 50.3 years, SD = 12.0, range 32 to 80; 62.0% females). The majority (59.9%) was recruited from the register of Frambu Resource Centre for Rare Disorders (Frambu). Frambu is one of nine state-financed centers administrated by the Norwegian National Advisory Unit on Rare Disorders. Frambu does not offer clinical assessment or follow-up. Registration in the database is voluntary and does not require medical referral. However, diagnostic confirmation from a medical institution is required to be registered. The remaining sample was recruited from the register of the Norwegian Union for Neurofibromatosis (NFFNF), a patient advocacy association. Questionnaires with prepaid postage were initially sent to the 189 persons with NF1 aged 30 years or older who were registered in Frambu's database. Four weeks later, the questionnaire was sent to 262 NFFNF members. Due to confidentiality, the Frambu and the NFFNF registers could not be combined. Thus, we do not know how many persons with NF1 are listed in both registers. Participants were explicitly asked to only respond once. Upon checking the consent forms, six participants had completed the questionnaires twice. We kept the forms with most completed answers and deleted the duplicates, resulting in 142 unique participants. As we do not know how many unique individuals the 189 + 262 forms were sent to, a response rate cannot be calculated. We do know that there is considerable overlap between the two cohorts.

Population data from the third wave of the epidemiological survey "Nord-Trøndelag Health Study" (HUNT3) was used as control group. HUNT3 is a comprehensive Norwegian

survey of health conditions (Krokstad et al., 2013). The HUNT study is a collaboration between HUNT Research Centre, (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. All inhabitants in Nord-Trøndelag County aged 19 years and above were mailed questionnaires and an invitation to a clinical examination. HUNT3 (2006-2008) comprises the latest population data, providing recent results for gender and age groups comparable to our respondents. The control group comprised 46,293 persons, that is, all participants aged 30 years and older from the third wave of HUNT3. The response rate in the HUNT3 control sample was 54%.

The study was planned and performed in cooperation with NFFNF patient advocacy group and approved by the Regional Committee for Medical and Health Research Ethics.

Instrumentation

The questionnaire comprised three main parts. Part 1 assessed background and demographic information (e.g., age and education level). Part 2 assessed health-related questions specific to the NF1 diagnosis compiled by the authors on the basis of current medical knowledge about NF1. This was done in collaboration with representatives from NFFNF. These questions concerned the NF1 diagnosis (e.g., time of diagnosis, relatives affected), NF1-typical physical symptoms (e.g., extent of neurofibroma), and activities of daily living. Controls did not receive Parts 1 and 2.

Part 3 consisted of excerpts from HUNT3, covering 11 domains in relation to mental and physical health and functioning reported by both the NF1 sample and controls. The 11 domains were: Comorbid diseases; Life satisfaction; Mental Health; Sleep; Pain; Gastrointestinal problems; Oral health; Memory problems; Social support; Alcohol Use; and Smoking.

Data analysis

1 Data were analyzed using IBM SPSS version 22.0. Comparisons between the NF1
2 sample and controls were computed by calculating Pearson's chi-square to estimate whether
3 frequencies were significantly different between the samples. Correlation and linear
4 regression analyses were applied to scaled variables from the NF1 sample. A Bonferonni-
5 corrected p -level of .004 was used as significance level to adjust for the number of zero order
6 correlations.
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13 Results

14 NF1 specific outcomes

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19 **Background.** See Table 1 for information on marital status, educational level, and
20 main source of income for the NF1 sample. Women had higher education than men ($p < .05$).
21 There were no other significant gender differences in terms of background variables.
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26 **Diagnosis.** The mean age of being diagnosed with NF1 was 22.9 years ($SD = 15.3$;
27 *range 0 to 69*). Just under half (48.6%) reported NF1 was genetically confirmed. One-third
28 (32.6%) reported it was not, and 18.8% reported they did not know. The majority (57.0%)
29 reported at least one family member also had NF1. With multiple categories possible, the
30 most frequently reported family members with NF1 were children ($n = 51$), siblings ($n = 30$),
31 mothers ($n = 30$), and fathers ($n = 13$).
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41 **NF1-specific physical symptoms.** Nearly all participants (96.5%) confirmed
42 neurofibroma, with 36.5% reporting having +100 neurofibromas. Major impact of
43 neurofibroma were reported by 11.6% to 22.5%, depending on neurofibroma location. The
44 percentages of participants who rated *major impact* of the following symptoms were: itching
45 (22.1%), scoliosis (10.9%), lung problems (8.6%), optic glioma (5.8%), and glomus tumors
46 (2.9%). The majority (69.8%) confirmed surgery related to NF1. From most to least frequent,
47 surgery was specified as for: neurofibroma (up to 71.2% depending on location), tumor(s)
48 affecting blood pressure (18.0%), and back surgery (12.6%).
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NF1-specific psychological symptoms. The percentages of participants who rated *major impact* of the following symptoms were: attention problems (24.3%), irritability (13.6%), hypoactivity (11.8%), impulsivity (9.5%), and hyperactivity (5.6%). Eleven participants (7.7%) confirmed diagnosis of attention deficit hyperactivity disorder (ADHD), and two participants confirmed currently taking medication for ADHD.

Activities of daily living. Most participants reported being able to perform a range of activities of daily living. The only activities more than 10 participants reported not being able to do were: driving (12.7%), complex household chores (9.9%), paying bills (7.1%), and taking the bus (7.0%). Thirty-one participants (21.8%) reported not having a driver's license.

The NF1 sample compared to controls.

Comorbid diseases. Half of the NF1 sample (50.0%) reported at least one comorbid disease (range 0-5). Both women and men with NF1 more frequently reported the following (past or current) diseases compared to controls: Mental problems (26.8%_{NF1} vs. 15.9%_{Cntrl}), asthma (19.0%_{NF1} vs. 11.5%_{Cntrl}), lung disease (i.e., chronic bronchitis, emphysema or COPD; 7.7%_{NF1} vs. 3.7%_{Cntrl}), epilepsy (7.7%_{NF1} vs. 1.7%_{Cntrl}), and other heart disease (7.0%_{NF1} vs. 3.7%_{Cntrl}); all $p < .05$. There was no difference between the samples for other diseases, with the following frequencies in the NF1 sample: hypertension (22.5%), degenerative joint disease (i.e., osteoarthritis; 11.3%), hand eczema (9.9%), cancer (9.2%), psoriasis (4.9%), fibromyalgia (4.2%), myocardial infarction (4.2%), angina pectoris (2.3%), stroke (2.3%), kidney disease (2.3%), diabetes (2.3%), arthritis (2.3%), Bechterew's disease (0.0%), Sarcoidosis (0.0%), and heart failure (0.0%)

HQoL. Both women and men with NF1 reported considerable more HQoL problems in most domains. See Table 2 for overview of the differences.

Gender differences within the NF1 sample

Fewer women than men with NF1 reported the positive mental health items (safe/calm, happy/optimistic), and more women reported to be lonely. More women than men reported to have sought help for mental health problems in the last year. Women with NF1 reported more sleep problems than men (except early waking) as well as more pain and bloating. See Table 2 for details. In terms of comorbid diseases, more women reported lung disease, and more men reported myocardial infarction. In fact, all NF1 participants reporting lung disease were women ($n = 11$), and all reporting myocardial infarction were men ($n = 6$).

Predictors of overall life satisfaction within the NF1 sample

See Table 3 for correlations between HQoL domains, age, and education within the NF1 sample. There were numerous significant associations between variables, indicating considerable overlap between HQoL domains. Notably, age was not significantly correlated with any of the HQoL domains, when corrected for multiple testing. Lower age was significantly associated with higher education, when corrected for multiple testing.

We entered all HQoL domains that were significantly correlated with life satisfaction after correction for multiple testing (i.e., mental health, sleep, pain, memory problems, and social support) in a linear regression model to predict life satisfaction. The model was significant ($p < .001$) and explained 42.3% of the variance in overall life satisfaction ($adj. R^2$). Only mental health was a unique significant predictor ($\beta = -.535, p < .0001$).

Discussion

In this cross-sectional survey, our expectation that HQoL problems are more frequent among persons with NF1 than population controls was largely supported. Our results are in line with previous findings showing that living with NF1 impacts multiple areas of functioning negatively, including HQoL (Bicudo et al., 2016; Crawford et al., 2015; Ferner et

al., 2017; Granström et al., 2012; Kodra et al., 2009; Page et al., 2006; Wolkenstein et al., 2001).

Our sample was recruited from non-clinical settings, but reported moderate to severe clinical severity of physical symptoms. A number of diseases were more prevalent among persons with NF1 compared to controls. These illnesses, specifically mental health problems, epilepsy, heart disease, lung disease including asthma, have also previously been described as more prevalent among persons with NF1 (e.g., Ferner et al., 2017; Ostendorf, Gutmann, & Weisenberg, 2013; Shino, Rabbani, Belperio, Lynch, & Weigt, 2012).

The finding of no difference between samples in ratings of having had/living with cancer is in contrast to other findings. Generally, in the younger NF1 population, malignant peripheral nerve sheath tumors are frequent, and in females breast cancer appears more frequently, earlier, and possibly with a worse prognosis than in controls (Howell, Hockenhull, Salih, & Evans, 2017). We believe the lack of difference in cancer frequency between persons with NF1 and controls have two main explanations. First, while the cancer risk is increased for younger persons with NF1, it increases with age in the normal population (Howell et al., 2017). Thus, larger differences may have been demonstrated if both samples were younger. Second, we did not distinguish between types of cancer, which may have masked risk differences for different types of cancer.

NF1 participants reported poorer mental health than controls. Several studies have identified increased mental health problems for persons with NF1, including increased prevalence of attention deficit hyperactivity disorder, depression, and anxiety (Barton & North 2004; Descheemaeker, Ghesquiere, Symons, Fryns, & Legius, 2005; Ferner et al., 2017; Hyman, Shores, & North, 2005; Mautner et al. 2002). It is uncertain to what extent complications from the NF1-gene may contribute to this increased prevalence, and to what

1 extent depression and anxiety in particular may be a result of living with NF1 and the
2 associated health challenges.
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4 Sleep problems were more prevalent among the NF1 sample compared to controls,
5 with nearly half of the NF1 sample confirming problems on at least one sleep item several
6 times per week. Reduced energy and vitality was reported by adults with NF1 in previous
7 studies (Kodra et al., 2009; Page et al., 2006; Wolkenstein et al., 2001). In a specific sleep
8 study of 114 adults with NF1, extremely high scores on all domains of the self-reported
9 Pittsburgh Sleep Quality Index (PSQI) questionnaire were identified for persons with NF1, all
10 significantly higher than norms (Leschziner, Golding, & Ferner, 2013). The authors also had
11 access to medical journals to identify potential causes for sleep problems, and identified pain,
12 anxiety, depression, cognitive issues, and organic sleep pathology as potentially
13 interacting/influencing factors (Leschziner et al., 2013).
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29 In the present study, pain was more prevalent among persons with NF1 than among
30 controls, with around two thirds of the NF1 sample confirming various forms of pain. Pain
31 has been a recurrent theme in quantitative and qualitative studies of persons with NF1
32 (Bicudo et al., 2016; Crawford et al., 2015; Ferner et al., 2017; Wolkenstein et al., 2001). Pain
33 in NF1 may be related to musculoskeletal manifestations such as osteopenia, scoliosis, and
34 more rarely to early complications as sphenoid wing or congenital tibia dysplasia (Kreask &
35 Walsh, 2016).
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46 Gastrointestinal complaints were more prevalent among persons with NF1 compared
47 to controls, with up to one-fifth of the sample reporting “much problems”. This is in line with
48 a recent study of 175 adults with NF1, which found more self-reported symptoms of
49 dyspepsia, irritable bowel syndrome, and constipation among persons with NF1 than their
50 relatives who were not affected by NF1 (Ejerskov, Krogh, Ostergaard, Fassov, & Haagerup,
51 2017). Physical gastrointestinal manifestations of NF1 range from localized microscopic
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proliferative lesions of autonomic nerves and interstitial cells of Cajal and diffuse microscopic ganglio/neuro/fibromatosis to grossly recognizable mass-forming neurofibromas and gastrointestinal stromal tumors, which are rarely considered in routine clinical practice and may be considerably under-recognized (Agaimy, Vassos, & Croner, 2012).

More than one-quarter of NF1 participants reported poor oral health, which was far more frequent than among controls. Previous studies have documented oral clinical manifestations for up to 70% of NF1 patients (Shapiro et al., 1984). Oral problems may be caused by gingival enlargement and pigmentation, dental abnormalities and/or caries, oral and perioral neurofibromas, and/or osseous lesions of the maxilla, mandible and the temporomandibular joint, which are all identified more frequently in the NF1 population (Javed et al., 2014).

The NF1 sample reported more memory problems than controls. Memory problems are among the neuropsychological challenges identified for persons with NF1, although most of this research has been conducted with children (Descheemaeker, Plasschaert, Frijns & Legius, 2013). In a study of 20 adults with NF1 recruited from a Belgian NF1 University clinic, Descheemaeker et al. (2013) identified poorer memory test results for persons with NF1 compared to IQ-matched controls, and concluded that problems with long-term auditory memory may be a specific NF1-related difficulty, beyond what is explained by generally lowered intellectual functioning. Poorer short term-memory function has also been identified in adults with NF1 compared to norms or controls (e.g., Ferner, Hughes, & Weinman, 1996; Zöller et al., 1997).

Fewer persons with NF1 confirmed having social support compared to controls, although it should be noted around 80% of persons with NF1 did confirm social support. In a study of 60 teenagers with NF1 recruited from a Danish center for rare diseases, teenagers with NF1 reported more loneliness than their non-NF1 siblings (Ejerskov, Lasgaard, &

Ostergaard, 2015). Lower social support from friends significantly predicted loneliness in this study. Loneliness was also more frequent among persons with NF1 in our sample compared to controls. To the best of our knowledge, no studies of adults with NF1 have addressed social support as a main variable. In a recent survey of 73 persons with NF1 aged 13 to 73 years, Rosnau et al. (2017) found higher self-esteem among persons who reported they had friends with NF1 and among those who took part in NF1 support groups.

We identified several gender differences between women and men with NF1. Overall, these differences reflect gender differences found in the general population (e.g., women typically experience more pain and sleep problems, drink less alcohol, and seek help for health problems to a larger degree than men) (e.g., Nelson, 2014; Michelson et al., 2000; Mong, & Cusmano, 2016). Women with NF1 reported less emotional support than female controls, with no difference between men with NF1 and male controls. More women than men with NF1 reported loneliness. As men generally report lower social support than women (Melchiorre et al., 2013), the difference identified in our sample may reflect that women with NF1 have higher expectations and/or requirement for social support than men. The gender differences identified regarding comorbid diseases also largely correspond to those identified in the general population. Only women with NF1 reported lung disease. Several pulmonary diseases are more common among women than men (Pinkerton et al., 2015). Only men with NF1 reported myocardial infarction. Myocardial infarction is more prevalent among men, and women have higher mortality from myocardial infarction than men (Mannsverk et al., 2012). Finally, more men than women with NF1 reported gastrointestinal complaints. This is in contrast to findings from the general population, in which women have more gastrointestinal complaints than men (Schmulson et al., 2010). This may indicate some gender-specific patterns regarding gastrointestinal complaints within the NF1 group that should be examined in future studies.

Unlike most previous studies examining HQoL in NF1, our participants were not recruited from clinical settings. Our results may therefore indicate that NF1 is associated with multiple HQoL challenges also for patients with less clinical severity. However, it should be noted that nearly all our participants reported neurofibroma, and half reported at least one comorbid disease. Therefore, the physical impairment experienced by our participants may be similar to that experienced by clinic-recruited persons with NF1. This may help explain why our findings regarding impaired HQoL are similar to previous clinic-recruited samples (e.g., Bicudo et al., 2016; Crawford et al., 2015; Ferner et al., 2017). Even when recruiting outside clinics, we may not be able to reach persons with NF1 with milder phenotypes. Such persons may choose not to register with NF1-related organizations, not to participate in research, or not be diagnosed with NF1 at all due having few clinical symptoms. This represents a challenge for future NF1 research.

We examined an older group of persons with NF1 compared to previous studies. Surprisingly, age was not significantly associated with any of the HQoL domains. This is in contrast to previous findings that older age predicts more HQoL problems in adults with NF1 (Kodra et al., 2009; Wolkenstein et al., 2001), but in line with another study in which age did not predict HQoL (Page et al., 2006). Our results suggest many health challenges have equal impact across the age span for persons with NF1. The negative correlation between age and education may imply that relatively younger persons with NF1 have better access to education than the older generation of persons with NF1.

Practice implications

We identified several significant associations between HQoL domains that have implications for practitioners. The main implication is that practitioners should address a wide range of health domains when counseling persons with NF1. Subsequently, some specific associations between HQoL domains identified herein can help provide priority guidelines for

practitioners. First, mental health was significantly associated with overall life satisfaction, sleep problems, memory problems, and social support. However, mental health was the only unique significant predictor of overall life satisfaction. Counseling or psychotherapy for mental health problems may thus be key priority to improve HQoL for persons with NF1. Second, sleep problems were significantly associated with life satisfaction, mental health, pain, gastrointestinal complaints, and memory problems. In line with Leschziner et al. (2013), this indicates that sleep problems are an intertwined part of NF1 problem presentation that should be addressed by practitioners. Third, the significant associations between pain, sleep problems, and gastrointestinal complaints indicate these domains may be an inherent part of other physical problems experienced by persons with NF1. Practitioners should explicitly address these domains to tailor physical health management plans for persons with NF1. Fourth, the increased prevalence of oral health problems identified indicates patient education about oral hygiene and frequent dental checks should be part of routine care for persons with NF1. Importantly, women with NF1 reported more frequent dental visits in the last year compared to controls, while men with NF1 did not. It may be particularly important to encourage men with NF1 to improve their dental care. Finally, social support was significantly associated with overall life satisfaction and mental health. Efforts should be made to identify characteristics of the minority of persons with NF1 who do not experience social support, to develop targeted interventions to increase their sense of social support.

Research recommendations

All domains investigated herein need to be examined further, and complimented with observation data beyond self-report. We also point to three specific areas in need of further investigation. First, our study showed one-quarter of the NF1 sample had sought help for mental health problems during the last 12 months, which was more frequent than for controls. However, this difference was significant for women only, and we do not have data on mental

health treatment access or outcome. Future studies should examine help seeking behavior among persons with NF1, as well their access to and outcomes of mental health treatment. Second, our results showed memory problems were significantly associated with poorer life satisfaction and mental health, as well as more sleep and gastrointestinal problems. Further studies of memory function in adults with NF1 and their role for NF1 presentation are needed. Finally, we identified several gender differences within the NF1 sample. Although most of these differences were in line with gender differences in the general population, future studies should examine gender differences with respect to gastrointestinal problems in NF1.

Study limitations

This study has some limitations to note. First, all data are self-reported and cannot be validated against more objective or functional data. For various reasons, persons with NF1 may both over- and under-report complaints. Second, although the sample is non-clinical, recruitment via a national advisory unit and a patient advocacy organization does not ensure generalizability. Third, we only included persons aged 30 years and older. A wider age range may have uncovered potential age effects on HQoL. Fourth, the data are cross-sectional, preventing us from inferring causal relationships between variables and following development of complaints over time.

Conclusions

In conclusion, health related QoL problems reported for persons with NF1 cover several medical domains and appear across the age span. The most recently published guidelines for diagnosis and treatment for NF1 (Ferner & Guttman, 2013) offer an excellent overview of medical treatments that may optimize health in persons with NF1. Given there is currently no cure for NF1 and that mental health problems were a key predictor of overall life satisfaction in our study, practitioners should also provide counseling addressing psychological aspects of living with NF1.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Compliance with Ethical Standards: All procedures performed in studies involving human participants were in accordance with the ethical standards of the Regional Committees for Medical Research Ethics and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all patients for being included in the study. This article does not contain any studies with animals performed by any of the authors.

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Table 1

Background variables for the NF1 sample

	Total	Women	Men
	(<i>N</i> = 142)	(<i>n</i> = 88)	(<i>n</i> = 54)
<u>Marital status</u>			
Single	33.8%	30.7%	38.9%
Married/cohabiting	57.7%	59.1%	54.6%
Divorced	7.7%	9.1%	5.5%
Widowed	0.7%	1.1%	0.0%
<u>Education level*</u>			
Primary school	6.3%	6.8%	5.6%
Secondary school	29.6%	29.5%	29.6%
High school	36.6%	29.5%	48.1%
< 3 years University degree	10.6%	11.4%	9.3%
> 3 years University degree	11.3%	17.0%	1.9%
Other/missing	5.6%	5.8%	5.5%
<u>Main source of income</u>			
Paid salary	45.1%	43.2%	48.2%
Disability pension	35.2%	38.6%	29.6%
Retirement pension	7.1%	6.8%	7.4%
Sickness benefits	9.1%	7.9%	11.2%
Other/missing	3.5%	3.5%	3.6%

Note. ¹Background information was missing for one participant. *Gender difference was significant at the .05-level (Pearson's chi-square).

NF1 HEALTH SURVEY

Table 2

Health-related quality of life in 142 persons with NF1 compared to 46,293 population controls

Total NF1 sample versus controls	Gender differences	
Health domain and frequency (<i>N</i> = 142)	NF1 women (<i>n</i> = 88) vs. female controls	NF1 men (<i>n</i> = 54) vs. male controls
Life satisfaction: At least <i>somewhat satisfied</i> = 57.1%	NF1 lower.**	NF1 lower.**
Mental health: <i>Mostly or very much</i> safe/calm (63.4%) [♂] , happy/optimistic (58.4%) [♂] , irritable (16.2%), lonely (14.1%) [♀] , nervous/uneasy (11.4%), anxious (12.0%).	NF1 less confident/calm,** happy/optimistic,** and more nervous/uneasy,** troubled by anxiety,**	NF1 less confident/calm*, and more nervous/uneasy*, troubled by anxiety*, irritable,**, and lonely.* No difference in
Sought professional help for mental health problems last year (26.8%).	irritable,** and lonely.** NF1 more help seeking for mental problems.*	help seeking for mental problems.
Sleep: At least <i>several times a week</i> daytime drowsiness (45.8%) [♀] , frequent night awakenings (40.8%) [♀] , trouble falling asleep (34.5%) [♀] , early waking (23.9%)	NF1 more problems falling asleep**, nightly waking,** early waking,** and daytime tiredness.**	NF1 more problems falling asleep**, nightly waking,* early waking,** and daytime tiredness.**
Pain: Confirmed (<i>yes/no</i>) general pain last six months (70.4%) [♀] , headache last year (69.0%) [♀] . Musculoskeletal pain last 3 months (62.0%) [♀] .	NF1 more general pain,** headache,** and musculoskeletal pain.**	NF1 more general pain*and headache.** No difference musculoskeletal pain.**

Gastrointestinal problems: Much problems with constipation (19.7%), bloating (16.9%) [♀] , alternating constipation/diarrhea (16.2%); diarrhea (12.0%); nausea (11.3%), heartburn (9.2%).	NF1 more nausea** and constipation.** No difference heartburn, diarrhea, or bloating.	NF1 more nausea,** diarrhea,* constipation,** and bloating.* No difference heartburn.
Oral health: At least <i>poor</i> (28.1%). Confirmed (yes/no) dental visit last year (83.8%).	NF1 poorer.** More frequent dental visits.	NF1 poorer.** No difference in dental visits.
Memory problems: <i>Much problems</i> with memory (8.5%).	NF1 poorer.**	NF1 poorer.**
Social support: Confirmed (<i>yes/no</i>) practical support (79.6%) and emotional support (83.1%)	NF1 less practical support** and emotional support.*	NF1 less practical support.* No difference emotional support.
Alcohol use: At least 2-3 times <i>pr. week</i> (14.1%), <i>never</i> (7.0%)	NF1 less alcohol use.*	No difference.
Smoking: <i>Daily</i> (15.5%)	No difference.	No difference.

Note. vs.=versus. ♂ more men than women within NF1 ($p < .05$). ♀ more women than men within NF1 ($p < .05$). *difference between NF1 and controls is significant at the $p < .05$ -level. **difference between NF1 and controls is significant at the $p < .001$ -level.

Table 3

Correlations between health-related quality of life domains in 142 adults with NF1

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.
1. Life satisfaction ⁺	1											
2. Mental health ⁻	-.64**	1										
3. Sleep problems ⁻	-.30**	.27**	1									
4. Pain ⁻	-.30**	.16	.48**	1								
5. Gastr. Problems ⁻	-.23*	.16	.29**	.35**	1							
6. Oral health ⁺	.18	-.08	-.06	-.20*	-.16*	1						
7. Com. diseases ⁻	-.22*	.05	.16	.20*	.22*	-.23**	1					
8. Memory prob. ⁻	-.35**	.36**	.42**	.18*	.24**	-.20*	.29**	1				
9. Social support ⁺	.40**	-.28**	-.20**	-.15	-.08	.08	.01	-.19*	1			
10. Alcohol use	.22*	-.02	-.09	-.17*	-.16	.24**	-.17	.02	.04	1		
11. Smoking	.08	.02	-.11	-.02	-.04	-.22**	.11	.01	-.17	.05	1	
12. Age	.14	-.05	.05	.03	-.10	-.16	.16	.01	-.06	.06	-.10	1
13. Education	.15	-.23**	-.12	-.08	.06	.14	-.21*	-.16	.12	.16	-.23**	-.33**

Note. Gastr. = gastrointestinal. Com. = comorbid. Prob = problems. ⁺higher scores indicate better health. ⁻higher scores indicate poorer health.

*correlation is significant at the $p < .05$ level. **correlation is significant at the $< .001$ level. Correlations in bold remain significant when adjusted for multiple testing (adjusted p -level = .004).