Fractures in women with eating disorders—Incidence, predictive factors, and the impact of disease remission

Cohort study with background population controls

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Title page

Title: “Fractures in women with eating disorders – incidence, predictive factors and the impact of disease remission: Cohort study with background population controls”

Short running: Fractures in eating disorders

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Abstract

Objective
Malnutrition and low weight in eating disorders (EDs) are associated with increased fracture risk compared to the general population. In a cohort study we aimed to determine fracture rates compared to age and gender matched controls (ratio 5:1), assess the impact of disease remission on fracture risk and establish predictive factors for fractures.

Method
803 ED patients referred to specialized ED treatment between 1994 and 2004 were included. In 2016, data on fractures were obtained through the Danish National Registry of Patients.

Results
Fracture risk was increased in anorexia nervosa (AN) (IRR 2.2 (CI 99%: 1.6-3.0)) but not in bulimia nervosa (BN) (IRR 1.3, ns) or other specified feeding or eating disorders (OSFED) (IRR 1.8, ns). IRR in the AN group were increased for vertebral fractures (IRR 3.8 (CI 99%: 1.4-10.3)), upper arm (IRR 3.0 (CI 99% 1.6-5.5) and hip (IRR 6.6 (CI 99 %: 2.6-18.0)). Disease remission in AN is associated to lower fracture risk compared to active disease, but higher fracture risk compared to controls (IRR 1.7 (CI 99 %: 1.1-2.7)).

In regression analysis, age at debut of disease, nadir BMI and duration of disease before referral to treatment, independently predicted fracture.
Conclusion

We confirm increased fracture risk in AN, and show significant differences in fracture risk between patients in disease remission and patients with active disease. Furthermore we show that age at debut of disease and duration of disease before referral to treatment is positively correlated to fracture risk, whereas nadir BMI is negatively correlated to fracture risk.

Clinical trial registration

The study is registered in ClinicalTrials.gov, number NCT00267228.

Keywords

Eating disorders, anorexia nervosa, bone mineral density, fracture, registries
Introduction

Malnutrition and low weight in eating disorders (EDs) are associated with a range of somatic complications affecting several organ systems, with one of the most prominent being bone. In anorexia nervosa (AN), hypogonadism, hypercortisolemia and growth hormone resistance are consistent features associated with decreased bone mineral density (BMD), even with a short duration of disease (Misra, Golden, & Katzman, 2015; Misra et al., 2011). Recently, the evolving technique of high-resolution peripheral quantitative computed tomography (HR-pQCT) has revealed decreased cortical thickness and impaired trabecular microarchitecture in the tibia and ultradistal radius, and the mechanical strength of the bone to be lower compared to healthy controls (Frolich et al., 2017; Singhal et al., 2018). Unsurprisingly, the risk of fracture has been reported to be around two times higher than in healthy subjects (Faje et al., 2014; Nagata, Golden, Leonard, Copelovitch, & Denburg, 2016; Vestergaard et al., 2002). As the debut of AN often coincides with puberty, a vital period for bone accrual, even short periods of severe malnutrition may result in irreversible bone loss and a life-long increase in fracture risk. This raises the question as to how the course of the disease and possible remission impacts fracture risk. As the majority of fracture studies rely solely on register-obtained data (Vestergaard et al., 2002), self-reported information on fractures and disease status (Faje et al., 2014) or simulation of bone strength (Bachmann et al., 2014), it can be difficult to discriminate early irreversible bone damage from the cumulative effect of chronic disease. Based on longitudinal studies of BMD, there is at least some evidence for an increase in BMD Z-scores upon weight-gain, but whether this reversibility applies to fracture risk, is not known (Viapiana et al., 2007).
Whereas bone loss and fracture risk previously has been investigated in AN, knowledge on bulimia nervosa (BN) and other specified feeding and eating disorders (OSFED) is sparse.

A few studies show decreased BMD in BN (Naessen, Carlstrom, Glant, Jacobsson, & Hirschberg, 2006; Newton, Freeman, Hannan, & Cowen, 1993) but diagnostic crossover (history of AN) and a high degree of heterogeneity among the studies, make interpretation difficult. In accordance, two recent meta-analyses agreed that the relationship between bone health and fracture risk in BN is unclear, and further research is warranted (Robinson, Aldridge, Clark, Misra, & Micali, 2016; Solmi et al., 2016).

From a clinical point of view, it is relevant to predict which patients have a particularly high risk of fractures. Well-established risk factors from studies in post-menopausal women, may not predict fracture in EDs. Potential predictive factors such as age at debut of disease, duration of amenorrhea, nadir weight and purging behavior have all been suggested as risk factors for fracture, but the majority of studies evaluates these proposed risk factors with the outcome being BMD, not fractures per se.

In this cohort study we therefore aim to (1) determine fracture rates in a cohort of Danish eating disorder patients compared to age and gender matched controls from the general population, (2) assess the impact of disease remission on fracture risk, and (3) establish predictive factors for fractures in the cohort. We hypothesized that BMD would be decreased in patients with AN or BN, that disease remission would decrease, but not normalize fracture risk and predictive factors for fracture would include early debut of disease and duration of disease.
Method

Subjects

Patients

A total of 803 female participants were recruited from a well-described cohort of all ED patients referred to specialized treatment at the Centre for Eating Disorders, Funen, Denmark, between January 1\textsuperscript{st} 1994 and December 31\textsuperscript{st} 2004 (Stoving, Andries, Brixen, Bilenberg, & Horder, 2011; Winkler, Bilenberg, Horder, & Stoving, 2015). The centre is the sole public facility treating EDs at the island of Funen, which is a demographically representative area of Denmark (Gaist, Sorensen, & Hallas, 1997). Upon referral, each patient underwent a diagnostic interview performed by both a psychiatrist specialized in EDs and an endocrinologist engaged in the treatment of somatic complications to EDs, in order to establish diagnosis and treatment course, including both nutrional rehabilitation and therapy. By the end of 2004, all medical charts were re-assessed for relevant variables as outlined in the data collection section.

The inclusion criterion for the present study was patients in the cohort diagnosed with either AN, BN or unspecified ED in the specified time frame, according to ICD-10 criteria. Exclusion criteria were male gender (due to a low number of patients) and residency outside the county of Funen, as these patients were referred from other eating disorder facilities, thereby making more severe disease, likely.

The study was approved by the local ethics committee (project-ID: S-VF-20050144) and the Danish Data Protection Agency (Journal.no. 2005-41-5578). Informed content were obtained at referral.
Controls

In order to establish relevant fracture rates for the general population an age- and gender (female) matched control group was randomly drawn from the Danish Civil Registry system, based on year and month of birth and gender. Each patient was matched with five controls.

Data collection

At referral (1994-2004):

Diagnoses were obtained according to the ICD-10 classification, and subsequently converted to DSM-V codes. Thus, AN patients were defined by body weight < 85 % of expected (median BMI for age and gender), fear of gaining weight and disturbed body image and BN by recurrent episodes of binge eating and inappropriate compensatory behavior in order to prevent weight gain (both > two times a week for three months). OSFED was defined as patients suffering from a clinical severe eating disorder, but not entirely fulfilling the criteria for AN or BN.

From interview, age at debut of disease and eating/purging behaviour was recorded. Height was measured on a wall-mounted stadiometer, weight on at calibrated platform scale and BMI was calculated as weight in kg divided by the square of height. As the cohort includes adolescents, percentage ideal body weight (% IBW) was calculated from median BMI for age and gender, based on reference values for 0-45 year old Danes measured between 1965-1983 (Nysom, Molgaard, Hutchings, & Michaelsen, 2001).

At end of clinical data collection (2004):
Medical charts were re-assessed for ED traits (ED diagnosis; treatment status; history of ED related admissions), anthropometrics (last recorded height and weight; nadir weight since referral), use of oral contraceptives, remission status and menstrual function. Menstrual status was classified as regular, irregular or non-existing (amenorrhea), based on a six-month period prior to follow-up. Assessment of remission-status was hampered by the fact that no consensus has been agreed upon regarding remission status in patients with EDs. Therefore, we classified patients as being in full remission when the following two criteria were met: (1) % ideal body weight (IBW) consistently above 85% and (2) no bulimic or purging episodes within the last six months (Stoving et al., 2012).

End of health database study (2016):

Information on fractures was obtained through the Danish National Registry of Patients (NRP), for both patients and controls. Data were retrieved through the Danish Health Data Authorities. The NRP contains diagnoses from all visits to public hospitals from 1977 and forward. In 1995, the NRP was expanded to include visits to outpatient clinics and emergency departments. The NRP is linked to the Danish Civil Registry System, providing a unique personal identification number to every Danish inhabitant, as well as information on migration out of Denmark and death. As records in the NRP are the basis of the hospitals reimbursements from the Danish Health Authorities, both coverage and positive predictive value of coding in the NRP is very high (>95%) (Thygesen, Christiansen, Christensen, Lash, & Sorensen, 2011).

The observation period for each patient (and the corresponding controls) was defined from referral to data extraction or restricted by either dead or migration out of Denmark. In case of diagnostic crossover between the three ED diagnoses, patients contributed observation time to intake diagnosis...
from referral to follow-up, and the follow-up diagnosis from follow-up to end of study. A potential problem regarding the NRP is that every procedure related to a fracture (assessment in the emergency room, X-ray, surgery, outpatient follow-up) generates a code that refers to the fracture. To avoid counting every procedure as incident fractures, we introduced a washout period of 180 days after first appearance of each fracture in the NPR (Hawley et al., 2016).

**Statistics**

Normality of baseline data was visually assessed using normal probability plots. Differences in baseline characteristics between ED groups were assessed with one-way ANOVA or the Kruskal-Wallis, depending on assessment of normality. If the overall p-value of the test was considered significant, differences between individual groups were assessed by Tukey-Kramer post hoc test for parametric data and Dunns test with Bonferroni correction, for non-parametric data. Categorical variables were compared using Fishers exact test. Differences between patients in remission and non-remission at follow-up were assessed using t-test or Wilcoxon-Mann-Whitney test, as appropriate. Missing data was regarded as missing completely at random and analysis were carried out only on complete cases; hence there was no imputation into the dataset.

Incidence rates (IR) were calculated as number of fractures divided by the observation time, and presented as number of fractures pr. 1000 patient/control years using the wash-out procedure described above to avoid the same fracture being counted more than once. Incidence rate ratios (IRR) were compared using Poisson regression; hence it was assessed whether the IRR between cases and controls were influenced by remission status. To decrease the risk of type 1 errors due to multiple comparisons, a 99 % confidence interval was used.
Finally, we assessed the impact of disease characteristics on fractures, by multiple logistic regression modelling. Potential variables included age, age at debut of disease, BMI at referral, nadir BMI, nadir IBW, duration of disease, duration of disease before referral to treatment and use of oral contraceptives. Variables entered the model if the p-value from univariate logistic regression was below 0.05, and kept in the model if the p-value of the variable in the model was below 0.1. Stata (Version 14.0, StataCorp, TX, US) was used for all statistical analysis.

**Results**

**Subjects**

A total of 1064 ED patients were eligible for inclusion (Figure 1). We excluded 66 patients due to out-of-county referral, 156 patients due to lack of data and 39 males, leaving 803 patients for further analysis. Patient characteristics at initial referral are shown in Table 1. AN patients were younger both at debut of disease and referral compared to BN patients (p<0.0001 for both), with no difference compared to OSFED patients. As expected, AN patients had markedly lower weight and BMI compared to both BN and OSFED patients (p<0.0001).

At the end of data collection, patient characteristics were stratified on remission status as shown in Table 2. In the AN group, patients in remission were younger and had a younger age at debut of disease (p-value 0.01 and 0.001, respectively) compared to patients with active disease. Furthermore, patients with active disease had lower nadir BMI and a higher prevalence of admission for treatment. In the BN group, no single characteristic differed between patients in
remission and patients with active disease. In the OSFED group, patients in remission had shorter
duration of disease, but otherwise comparable with patients in remission.

The amount of missing data was below 5 % for all characteristics, except for nadir BMI (3 % in
AN; 16 % in BN and 19 % for OSFED).

Fractures

Table 3 shows the absolute number of fractures, fracture incidence rates and incidence rate ratios
compared to controls. Median follow-up time was 19.3 years (IQR 16-22) for AN, 20.7 years (IQR
19-22) for BN and 17.7 (IQR 15-22) for OSFED. Overall, fracture risk was increased in AN (IRR
2.2), but not in BN (IRR 1.3, ns) or OSFED (IRR 2.0, ns). Split into separate fracture categories,
IRR in the AN group were increased for vertebral fractures (IRR 3.8), upper arm (IRR 3.0) and hip
fractures (IRR 6.6). In the BN and OSFED groups, no single fracture type incidence was
significantly different to controls.

Impact of disease remission

In the AN group, the increased overall fracture risk was largely down to increased fracture risk in
the group of patients with active disease (IRR 2.6 vs. 1.7 in the remission group, p<0.05). The
difference was most pronounced for hip (IRR 9.8 vs. 2.9, p<0.05) and vertebral fractures (IRR 5.6
vs. 3.8, p<0.05), and non-exiting for forearm and lower leg fractures. Remission-status had no
impact on fracture risk in neither BN nor OSFED.

Risk factors
The result of the regression modelling is reported in table 4. Age at debut of disease, nadir BMI and duration of disease before treatment were all significantly associated with fracture risk, and hence, included in the model. Use of oral contraceptives entered the initial model, but was removed (in-model p-value=0.16). Age at first referral was omitted due to collinearity with age at debut of disease.

Evaluation of the model returned an area under the receiver-operating curve of 0.70 and an $r^2$ value of 0.12.

**Discussion**

This study of a well-described ED cohort with extensive information on disease characteristics is the first study to address the impact of disease remission on fracture risk in EDs. We confirm that fracture risk is increased in women with AN, and show that there are significant differences in fracture risk and patterns of fractures between patients in disease remission and patients with active disease. Furthermore, we show that age at debut of disease and duration of disease before referral to treatment is positively correlated to fracture risk, whereas nadir BMI is strikingly negatively correlated to fracture risk.

In female patients with AN, we report an overall IRR compared to age-matched controls of 2.2 (CI 95%: 1.7-2.6), resembling results reported from both Danish and international cohorts (Faje et al., 2014; Nagata et al., 2016; Vestergaard et al., 2002). The patients in our study are recruited from a highly-specialized treatment facility, introducing a possible selection bias compared to the entire ED population, which might explain why fracture risk in our sample is higher than reported from population studies based on self-reported data. Fractures of upper arm and elbow, lower arm and
wrist and lower leg, were the most frequent fractures in both patients and controls, consistent with other studies (Vestergaard et al., 2002). Looking further into specific fractures, IRR were markedly increased for classical osteoporotic fractures, including vertebral and hip fractures. This highlights a relevant issue of absolute vs. relative fracture risk. The absolute rates for both fracture types are low (1.7 and 2.5/1000 patient years, respectively), but compared to a much lower incidence in young healthy women, the relative risk is significantly increased. This should be taken into account, especially when communicating the extent of the issue to patients and relatives.

In BN and OSFED, the IRRs of total fractures as well as the independent fracture types were between 1 and 2, indicating increased fracture risk, but the apparent increase was insignificant. Again, our challenge was the low number of fractures, providing to little power to reach statistical significance. Thus, although there were trends towards increased fracture risk in both BN and OSFED, no conclusions can be made, based on our data.

In the group of recovered AN patients, the IRR for overall fractures was lower compared to patients with active disease. It is important to emphasize that we were not able to compare fracture rates before and after disease remission, simply because of the low number of fractures. Instead, the disease remission status applies to a group of patients with shorter duration of disease, higher nadir BMI, a lower number of ED-related hospital admissions and a minimum of six months of BMI above 85% of expected prior to follow-up. Thus, the cumulative burden of disease is very likely to differ between the two groups. Except for forearm fractures, all fracture types appeared more frequently in the non-remission group, with the difference being most pronounced for vertebral and
hip fractures. The idea of fracture risk being positive correlated to cumulative burden of disease is supported by our regression analysis. We establish nadir BMI and duration of disease before treatment, as important risk factors, offhand intuitive, but non-the less, not shown before. The fact that age at debut of disease is positively correlated to fracture risk, is not a surprise since increasing age at debut is a well-known risk-factor for poor outcome in AN (Zipfel, Lowe, Reas, Deter, & Herzog, 2000). It should be acknowledged, however, that the performance of our regression model is moderate, with an AUC of just 0.70. This result illustrates that there is much more to fracture risk, than we are able to establish. Potential additional risk factors includes level of physical activity, smoking, calcium and vitamin D deficiency, use of antidepressants and genetics, none of which we were able to include in the model.

Taken together, our results imply that increased fracture risk is a particular problem in patients with long-lasting severe AN, but as important, that fracture risk is considerably lower in patients who remit even after several years of severe disease.

A number of strengths and limitations apply to the study. The obvious strength of the study is our extensive data on weight at referral, nadir weight and the repeated assessment of diagnosis through the course of the ED. It does not fully eliminate issues related to remission/relapse and diagnostic crossover, but we were able to account for early diagnostic instability. Another important strength is our fracture data obtained from the NRP. Since Danish patients suspected for bone fracture are referred solely to public hospitals, both coverage and validity is high. With a mean follow-up of
more than 18 years, we suspect that obtaining similar information on fracture type and timing in relation to the ED diagnosis by self-report, would have been inaccurate at best.

Important limitations include the lack of a more widely accepted definition of disease remission. We chose to focus our criteria on bodyweight and purging behavior. From a patient perspective, disease remission is much more complex, due to the psychological symptoms (fear of weight gain, body dissatisfaction), but as these factors does not directly affect bone metabolism, the association between fracture risk and remission would have been deluded somewhat. Furthermore, we chose not to include resumption of menses in the definition of remission, even though estrogen clearly is anabolic to bone. The problem is, that resumption of menses is unpredictable and could be delayed for months or even years after normalization of body-weight (El Ghoch, Calugi, Chignola, Bazzani, & Dalle Grave, 2016). As a consequence, amenorrhea is omitted from the DSV-5 criteria for AN, which to some degree validates our decision.

Another limitation is the lack of data on behavioral factors such as physical activity. Patients were advised to decrease their level of physical activity as part of their treatment program, but since patients predominantly were treated in an outpatient setting, we were not able to measure compliance. Failure to successfully limit excessive physical activity, could very well contribute to the significant difference in fracture risk between patients with active disease and patients in remission.

This study does not include males, since the number of male patients in the cohort was very limited and the subgroup of male patients differed according to disease course (Stoving, Andries, Brixen, Bilenberg, & Horder, 2011). Due to gender differences in normal bone development during
adolescence our results do not apply to male patients. Future studies in the understudied population of male ED patients are highly warranted.

Conclusion

In conclusion, we report increased fracture risk in women with AN, but not in BN and OSFED. AN patients in remission had lower fracture risk compared to patients with active disease, but increased risk compared to age-matched healthy controls. Furthermore, we establish age at debut of disease, nadir BMI and duration of disease before treatment, as important risk factors for fracture. Efforts towards early nutritional rehabilitation and weight gain is likely to be the most effective instrument towards reduction of fracture risk in AN.
<table>
<thead>
<tr>
<th></th>
<th>AN (n=424)</th>
<th>BN (n=251)</th>
<th>OSFED (n=128)</th>
<th>AN vs. BN</th>
<th>AN vs. OSFED</th>
<th>BN vs. OSFED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>18 (15; 21)</td>
<td>21 (18; 24)</td>
<td>19 (16; 24)</td>
<td>&lt;0.0001</td>
<td>0.12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Age at debut of disease (y)</strong></td>
<td>15 (13; 18)</td>
<td>16 (15; 19)</td>
<td>16 (14; 19)</td>
<td>&lt;0.0001</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>1.65 ± 0.07</td>
<td>1.68 ± 0.07</td>
<td>1.67 ± 0.07</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
<td>0.50</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>44.2 ± 7.3</td>
<td>60.0 (53.9; 67.0)</td>
<td>58.0 (52.1; 64.0)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>16.2 ± 2.1</td>
<td>21.0 (19.2; 23.5)</td>
<td>20.2 (19.2; 22.6)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>%IBW</strong></td>
<td>80.9 ± 11.4</td>
<td>101.2 (92.8; 112.7)</td>
<td>99.6 (94.2; 111.8)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Purging behaviour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxatives (n, %)</td>
<td>18 (4)</td>
<td>24 (9)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
<td>0.43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Vomiting (n, %)</td>
<td>48 (11)</td>
<td>220 (88)</td>
<td>12 (9)</td>
<td>&lt;0.001</td>
<td>0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive (n, %)</td>
<td>337 (79)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Binge/purging (n, %)</td>
<td>86 (21)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Table 1 Baseline characteristics according to diagnosis. p>0.05 is considered significant. N/A: not applicable
<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
<th>p-value</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nadir BMI</strong></td>
<td>15.5 ± 1.9</td>
<td>14.4 (2.4)</td>
<td>&lt;0.0001</td>
<td>19.1 (17.9; 21.0)</td>
<td>18.7 (17.0; 21.2)</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Nadir %IBW</strong></td>
<td>77.4 ± 10.4</td>
<td>71.3 (12.7)</td>
<td>&lt;00001</td>
<td>91.8 (86.2; 102.0)</td>
<td>92.0 (82.2; 101.4)</td>
<td>0.67</td>
</tr>
<tr>
<td><strong>Duration of disease (y)</strong></td>
<td>3 (2; 6)</td>
<td>4 (2; 7)</td>
<td>0.47</td>
<td>4 (3; 7)</td>
<td>5 (3; 8)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>History of at least one admission (%)</strong></td>
<td>73 (38)</td>
<td>113 (49)</td>
<td>&lt;0.01</td>
<td>1 (1)</td>
<td>23 (12)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

Table 2 Characteristics at follow-up, stratified on remission status. % IBW: % ideal body weight.
<table>
<thead>
<tr>
<th></th>
<th>AN</th>
<th></th>
<th>BN</th>
<th></th>
<th>OSFED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>IR/1000 patient years (CI 95 %)</td>
<td>IRR compared controls (CI 99 %)</td>
<td>n</td>
<td>IR/1000 patient years (CI 95 %)</td>
</tr>
<tr>
<td><strong>All fractures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>107</td>
<td>13.4 (11.1-16.3)</td>
<td><strong>2.2 (1.6-3.0)</strong></td>
<td>36</td>
<td>6.7 (4.8-9.3)</td>
</tr>
<tr>
<td>Remission</td>
<td>39</td>
<td>10.7 (7.8-14.6)</td>
<td><strong>1.7 (1.1-2.7)</strong></td>
<td>13</td>
<td>7.5 (4.3-13.2)</td>
</tr>
<tr>
<td>Non-remission</td>
<td>68</td>
<td>15.9 (12.5-20.1)</td>
<td><strong>2.6 (1.8-3.7)</strong>*</td>
<td>23</td>
<td>6.8 (4.5-10.2)</td>
</tr>
<tr>
<td><strong>Vertebral</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
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<td>14</td>
<td>1.7 (1.0-3.0)</td>
<td><strong>3.8 (1.4-10.3)</strong></td>
<td>3</td>
<td>0.6 (0.2-1.7)</td>
</tr>
<tr>
<td>Remission</td>
<td>3</td>
<td>0.8 (0.3-2.5)</td>
<td>1.8 (0.2-8.2)</td>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-remission</td>
<td>11</td>
<td>2.5 (1.4-4.6)</td>
<td><strong>5.6 (1.8-16.0)</strong>*</td>
<td>1</td>
<td>N/A</td>
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<tr>
<td><strong>Upper arm</strong></td>
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<td>All</td>
<td>30</td>
<td>3.8 (2.6-5.4)</td>
<td><strong>3.0 (1.6-5.5)</strong></td>
<td>7</td>
<td>1.3 (0.6-2.7)</td>
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<tr>
<td>Remission</td>
<td>13</td>
<td>3.6 (2.1-6.1)</td>
<td><strong>2.8 (1.1-6.2)</strong></td>
<td>2</td>
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<td>Non-remission</td>
<td>17</td>
<td>4.0 (2.5-6.4)</td>
<td><strong>3.1 (1.4-6.5)</strong>*</td>
<td>5</td>
<td>1.5 (0.6-3.5)</td>
</tr>
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<td><strong>Forearm</strong></td>
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<td>28</td>
<td>3.5 (2.4-5.1)</td>
<td>1.6 (0.9-2.9)</td>
<td>12</td>
<td>2.2 (1.3-3.9)</td>
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<td>Remission</td>
<td>15</td>
<td>4.1 (2.4-6.8)</td>
<td>1.9 (0.8-3.9)</td>
<td>6</td>
<td>3.7 (1.7-8.3)</td>
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<td>3.0 (1.8-5.2)</td>
<td>1.4 (0.6-3.0)</td>
<td>5</td>
<td>1.5 (0.6-3.5)</td>
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<tr>
<td><strong>Hip</strong></td>
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<td><strong>6.6 (2.6-18.0)</strong></td>
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<td>4</td>
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<td>2.9 (0.4-12.3)</td>
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</tr>
<tr>
<td>Non-remission</td>
<td>16</td>
<td>3.7 (2.2-6.1)</td>
<td><strong>9.8 (3.6-27.7)</strong>*</td>
<td>1</td>
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<tr>
<td>Variable</td>
<td>OR</td>
<td>SE</td>
<td>CI 95%</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>---------------------------</td>
<td>------</td>
<td>------</td>
<td>---------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Duration of disease before referral</td>
<td>1.10</td>
<td>0.03</td>
<td>1.045 - 1.16</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Age at debut of disease</td>
<td>1.10</td>
<td>0.03</td>
<td>1.05 - 1.15</td>
<td>&lt; 0.001</td>
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</tr>
<tr>
<td>Lowest BMI since referral</td>
<td>0.88</td>
<td>0.05</td>
<td>0.80 - 1.00</td>
<td>&lt; 0.05</td>
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</tr>
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</table>

Table 4. Multiple logistic regression modelling of risk factors for fracture in AN. AROC 0.70; R² 0.12. OR: Odds ratio; SE: standard error of the mean.

Table 3: Absolute number of fractures, fracture rates and IRR compared to controls, stratified by remission status. Categories with less than three fractures are omitted due to large insecurities of the estimates. Values in bold indicate significant difference compared to controls. * p-value < 0.05 on the difference between remission and non-remission from Poisson regression analysis.
Figure legends

Figure 1: Inclusion flow
References


disorders--a nationwide register study. *Int J Eat Disord, 32*(3), 301-308. doi: 10.1002/eat.10101


Baseline - 1994-2004

FANS cohort
n=1064

Out-of-county referrals
n=66

Study population
n=998

Cases re-assessed
n=998

Insufficient data on weight
n=104

Insufficient diagnostic information
n=52

Male gender n=39

End of data collection - 2004

Fracture data
n=803

AN = 424
BN = 251
OSFED = 128

End of study - 2016

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