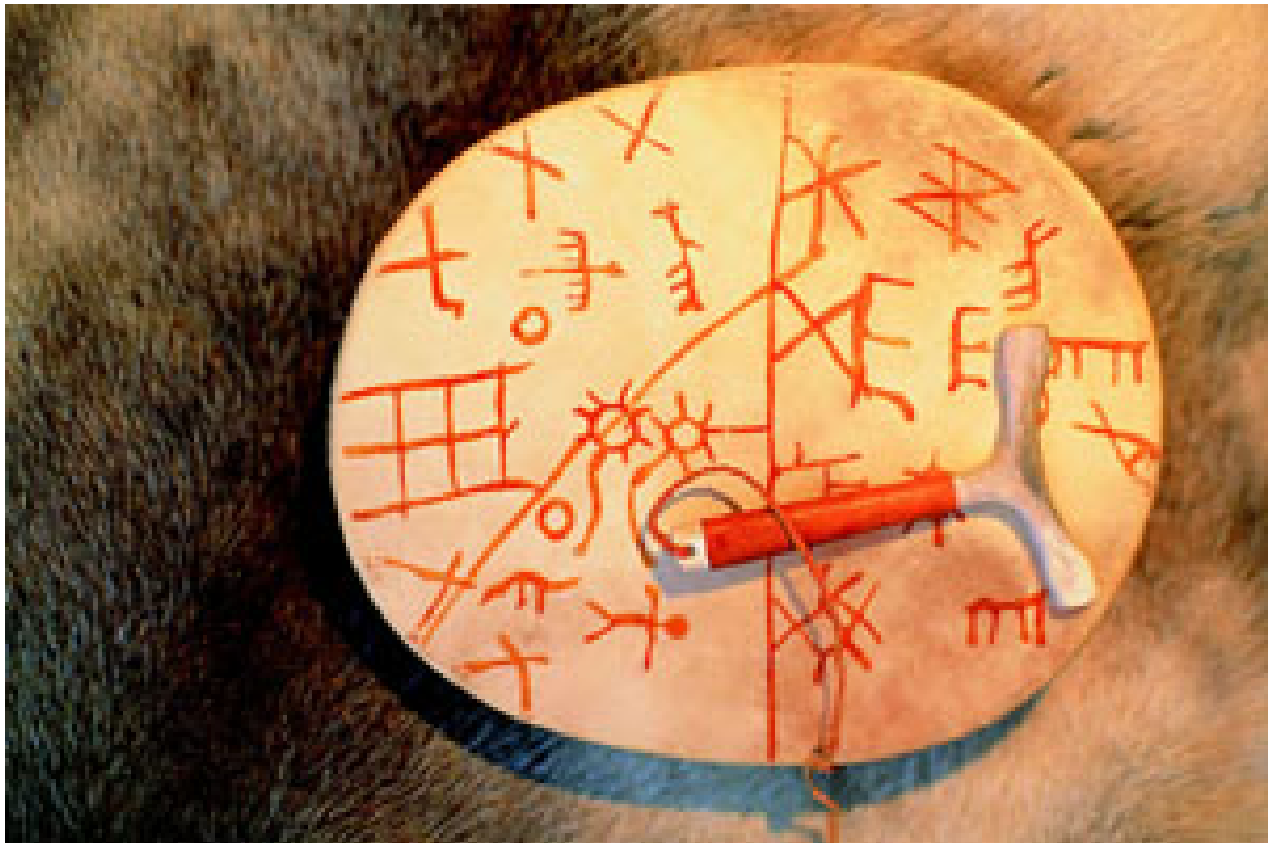


**Ankylosing spondylitis, aortic regurgitation, acetabular dysplasia and osteoarthritis of the hip.
An epidemiological survey in a Norwegian Sámi population**

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I began to write this thesis in 1991, and published my first article in 1992. The work was interrupted in the mid-1990s for various reasons.

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Our beloved children, Sverre, Lasse and Kajsa, for being inspiring fellow human beings.

2. List of papers

1. Knut Johnsen, Jan Tore Gran , Knut Dale and Gunnar Husby. The prevalence of ankylosing spondylitis among Norwegian Samis (Lapps). *J Rheumatol* 1992; 19(10):1591-1594
2. Knut Johnsen, Per Lunde and Markku Mähönen. Prevalence estimation and follow-up of aortic regurgitation subjects in a Norwegian Sámi population. *Scandinavian Cardiovascular Journal* 2008, accepted 4 October 2008, (2008 Nov 8:1-5, epub ahead of print).
3. Knut Johnsen, Rasmus Goll and Olav Reikerås. Acetabular dysplasia in Sámi population: a population study among Sámi in north Norway. *International Journal of Circumpolar Health* 2008; 67(1);147-153
4. Knut Johnsen, Rasmus Goll and Olav Reikerås. Acetabular dysplasia as an aetiological factor in development of hip osteoarthritis. *International Orthopedics*, accepted: 28 February 2008, (2008 May 14, epub ahead of print).

3. Abbreviations

AC	Accuracy
AD	Acetabular dysplasia
AR	Aortic regurgitation
AS	Ankylosing spondylitis
CDE	Colour Doppler echocardiography
CDH	Congenital dislocation of the hip joint
CE angle	Centre-edge angle
CI	Confidence interval
DDH	Developmental dysplasia
HLA	Human leukocyte antigen
NPV	Negative predictive value
OA	Osteoarthritis
PPV	Positive predictive value
SE	Sensitivity
SP	Specificity

4. Introduction

It has previously been documented that HLA-B27 is present in about 26% of the Sámi population in northern Norway(1). In the Caucasian populations of North America and Europe the population prevalence of the disease susceptibility antigen HLA-B27 is approximately 6-10%, while in southern Norway it is 10% (2-5). The Chinese and African-American populations have a prevalence of about 2%, while the Japanese population has only 0.2% (4). The general Finnish population has a B27 prevalence of 14%. In the Caucasian population of Tromsø, northern Norway, 16% were HLA-B27 positive, which indicates a significant genetic contribution from the Sámi and Finnish populations (1;5). It also seems that the Arctic peoples have the highest prevalence of HLA-B27. The prevalence of this genetic marker among the Haida Indians in Canada (6) is one of the highest that has been reported (50%). But other Arctic populations, too, e.g. the Inuits, have an HLA-B27 frequency of over 30%. (6;7).

The association between the immunologic marker HLA-B27 and AS was first reported by two groups in 1973 (8;9). It became clear that HLA-B27 was common in the entire group of seronegative spondyloarthropathies, especially for AS. This gene is present in more than 90% of AS patients (4;7). Today, at least 23 subtypes of HLA-B27 have been identified (B2701-B2723), and B2706

(native Indonesians) and B2709 (Sardinians) may not be associated with AS (10).

In previous studies the prevalence of AS seems to correspond roughly to the frequency of HLA-B27 in the population (7;11). The highest prevalence of AS is demonstrated in areas with the highest B27 frequencies (among the Haida Indians in Canada: 6% AS and 50% HLA-B27) (7). The lowest prevalence of AS is found among the Japanese, among whom the prevalence was estimated to be less than 1/200 as compared with Caucasians (12). The strength of the association between HLA-B27 and AS in different races seems to vary. In the Turkish population HLA-B27 was present in 70% of AS subjects (13), and among Greeks 81% (14).

An exception to this general association between HLA-B27 and AS is found in Gambia, where HLA-B27 prevalence was 6%, but AS prevalence was 0% in age groups over 25 years. This could not be explained by referring to subtypes of HLA, and a theory was postulated that this population may have a protective factor against AS disease that is located outside the HLA-B27 system, or that there are genetic factors operating, supporting the theory that some ethnic populations may be genetically protected against AS (15).

However, the aetiology and pathogenesis of AS are still unclear and poorly understood. According to various theories, immune-mediated mechanisms involving HLA-B27, inflammatory cellular infiltrates, cytokines and genetic and environmental factors may all play a part in the pathogenesis of this disease (10;16). No specific cause of the disease has ever been discovered, but an association between AS and inflammatory bowel disease suggests that enteric bacteria may play a part (10;17;18).

The HLA-B27 associated rheumatic diseases, especially AS, have long been known to be associated with cardiac complications, mainly aortic regurgitation (AR) and atrioventricular conduction blocks (4;19). One study has shown a significant association between HLA-B27 and a combination of aortic regurgitation and severe conduction system abnormalities (88%), regardless of whether the patients in question have AS, so-called HLA-B27-associated syndrome (19). But there seems to be less of an association between AR and HLA-B27 antigen (15-20%) (4). However, it is still unclear whether AR is independently associated with HLA-B27, because of diverging reports in the literature (20-22).

It was also interesting to map the Sámi hip in a population-based study and to evaluate the complications of developmental dysplasia of the hip (DDH), especially because the incidence of DDH has been reported to be frequent in the

Sámi population as compared with the general Western European population (23;24). DDH refers to a continuum of abnormalities in the immature hip that can range from subtle acetabular dysplasia (AD) to congenital dislocation (CDH), i.e. an intracapsular displacement of the femoral head prior to, or shortly after, birth (25;26). The pathophysiology and natural history of the range of morphological and clinical disorders that constitute developmental dysplasia of the hip are poorly understood. It is probably polygenetically inherited, as many studies have shown that up to 25% of cases can be explained by hereditary factors (24). But specific heritability factors have never been estimated (27). There are also racial variations (28;29) with an uneven geographic distribution (24;30-34). Apart from the Sámi, the highest prevalence occurs in Asia (see Paper 3). However, CDH prevalence varies greatly from one country to another, with an especially high prevalence in Slavic populations (24). In the Czech Republic, northern Italy, southern Germany and Japan, CDH prevalence varies from 2 to 5% (35), but it is rare in China, i.e. morbidity rates among Asians vary. Interestingly, the Orientals, except for the Japanese, have a higher prevalence of AD, but a lower prevalence of CDH than the white European populations (34;36). CDH is also very common among the Native Americans (Apaches and Navahos) and the native Canadians, approximately 5% (37).

There have been disagreements about the aetiology of the high prevalence of DDH among the Sámi. On the one hand there are spokesmen for the hereditary

theory, but on the other there are those who believe in a mechanical aetiology. Sámi cradle theory has been used to explain the high prevalence of DDH among Sámi since Wessel's publication in 1918 (23). Before World War I, it was very common for Sámi children to spend their first year of life in a cradle. When lying in a Sámi cradle the hips are forced into a maximally negative position, with full adduction and extension and internal rotation. This position could be a possible reason for a predisposed dislocation, if not the main reason for the development of this disease. This explanation is supported by the fact that the North American Indians had the same tradition as the Sámi of swaddling their children and placing them in a cradle (38).

The Sámi population examined in this study lives north of the Arctic Circle, where the sun disappears totally for several months every year, and a possible link between a lack of vitamin D, vitamin D receptor polymorphism and DDH is suspected (39). Keeping in mind that the protective action of vitamin D on some diseases (40;41) is mediated through vitamin D receptor binding (42), it can be speculated that inadequate vitamin D intake in former generations of Sámi people might have resulted in genetic selection for vitamin D receptor polymorphism and DDE in the contemporary Sámi population. However, no studies on vitamin D intake and/or vitamin D polymorphism in the Sámi population have been carried out.

OA prevalence is increasing rapidly and its incidence increases with age (43). Although OA has a characteristic clinical course and distinctive radiology, the aetiology is still unclear and it is considered a multifactor disease. It is unclear whether OA is a single entity or a manifestation of different diseases that share a common pathological pathway (44;45). It has been assumed that systemic factors are the main cause, but that local biomechanical factors, unique for each joint system, play the decisive role in determining the severity of the disease (46). Joint incongruence due to DDH has been found on radiographs of many patients who have degeneration of the hip joint (47;48), and marked AD has therefore been considered a major etiologic factor (25;26). However, the relationship between the severity of AD and the rate of OA development is less clear. Few longitudinal studies exist. Wiberg (47) found a linear relationship between CE angle and the age of onset of hip OA. Seven of 17 hips in Wiberg's study were subluxated and the rest had a very small CE angle, a mean angle of 10 degrees. Cooperman (49) performed a similar study, but without any cases of subluxation and with a mean CE angle of only 7.4 degrees. He could not prove that there was a linear relationship between the CE angle and the rate at which OA developed. In Wiberg's study subluxation appeared to be the main factor leading to early OA (49). Hasegawa's (50) follow-up study showed that CE angles smaller than 10 degrees were significant predictors for hip OA, but he used subchondral sclerosis, which can also be regarded as a normal aging phenomenon, as a cardinal radiographic feature of OA. Background incidence of

hip OA and the influence of age and sex in these studies were not taken into consideration.

Because of advances in reconstructive hip surgery (51-54), the need for a clear understanding of the natural course of AD is more important than ever.

Acetabular dysplasia is probably polygenetically inherited (27;55), but few population studies have been published on this subject (28;29;33;34;56;57).

Also, studies of the natural history of untreated dysplastic hips are few, and those available do not provide objective prognostic guidelines (48;49). In the available literature on the influence of hip dysplasia on the development of hip OA, only a few studies investigated the influence of this parameter in a prospective cohort design with a long follow-up period (48;49;58;59).

The risk for development of hip OA varies widely in different populations, from 1- 4% in adult black populations to 5-11% in white populations, with the highest prevalence among older people (34;60;61). It is well known that in the Sámi population there is a high prevalence of hip problems. Wessel (23) performed a systematic skeletal study of Sámi in the county of Finnmark in 1918, and he found that 5% of the population had dislocated hips. Getz (24) undertook a skeletal study of approximately 300 Sámi in 1956, and he found that 4% had dislocated hips. The CE angle was described in 1939 by Wiberg as quantifying acetabular dysplasia in adults (47). According to Wiberg, CE angles greater than

24 degrees are normal, angles between 20 and 24 degrees are subnormal or slightly dysplastic, and angles below 20 degrees are defined as dysplastic.

On the basis of all these considerations a cross-sectional population-based study of two Sámi municipalities, Karasjok and Kautokeino, was undertaken.

5. Aims of the study

The aims of the present population-based study among the Sámi were:

1. To investigate the prevalence of HLA-B27 and
 - a. the relation to ankylosing spondylitis
 - b. the impact of these on aortic regurgitation
 - c. the progression rate of aortic regurgitation during 15-17 year-follow-up.
2. To investigate the prevalence of acetabular dysplasia and hip osteoarthritis and the etiologic relation between acetabular dysplasia, back pain and hip osteoarthritis.

6. Methodology

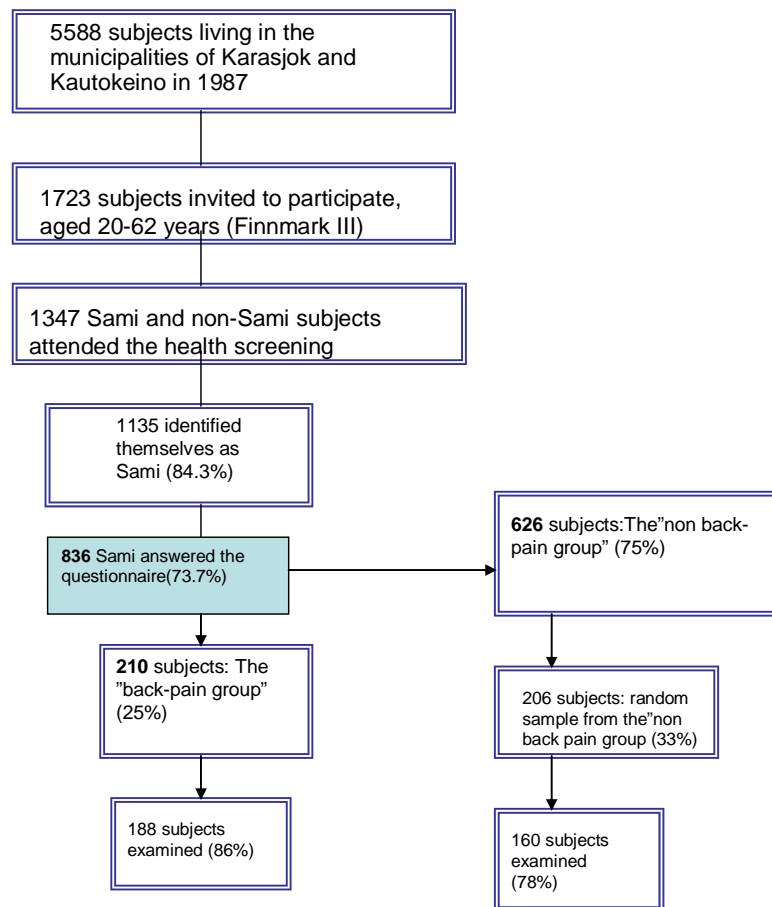
Survey location: The present study was performed in a Sámi core area, the municipalities of Karasjok and Kautokeino, in the county of Finnmark, northern Norway, which is located at a latitude of 69-70 degrees north and covers an area of 15 168 km². These two municipalities are located in a high-lying inland area of the county. Reindeer herding was in 1990-1991 one of the main occupations in the area, but agriculture, small industry and tourism are also important trades.

In 1987 there were 5588 inhabitants in these municipalities, and the population existed roughly of three ethnic groups: the Sámi, Finns and ethnic Norwegians. The Sámi are the majority population, and in 1987 84.3% of the population in these municipalities was Sámi (Paper 1). Their age distribution is shown in Table I, Paper 1.

The Sámi are indigenous people of northern Scandinavia and the Kola Peninsula. Approximately 50-70 000 of Norway's inhabitants are Sámi. The Sámi are to some extent genetically mixed with other Scandinavian populations, but genetic distinctions can still be traced. In certain areas such as inner Finnmark (the Sámi core area), the population was quite isolated and stable until the early 1970s, and the Sámi have always been in the majority. The rate of immigration to these areas has generally been low, and has been less than the

emigration rate. Nevertheless, the population has increased due to a high birth rate. The Sámi language has been preserved best in these areas, and ethnic language skills reflect genetic background to a large extent. Self-perceived ethnicity, particularly a half-generation ago, also reflects the genetic background. In the remainder of northern Norway, the Sámi people were subjected to rigorous linguistic and cultural assimilation policies, which resulted in a substantial loss of ethnic identity and language skills. In these areas a more nuanced definition of ethnicity is needed, based on ethnic language skills in earlier generations. In the Ung i Nord study and the SAMINOR study (62) (63) the participants were asked about the mother tongues of their grandparents, their parents and themselves. They were also asked to define their own ethnic identity as well as that of both their parents. Such a detailed questionnaire with regard to ethnicity in inner Finnmark would not have been of greater value than the questionnaires used in our study in 1987. We simply asked the participants about their ancestry: Are two or more of your grandparents of Sámi origin?

Figure 1. Flow chart overview of the survey among the Sámi



Population survey: An epidemiological survey was undertaken in 1987 (Finnmark III) with the main purpose of investigating possible cardiovascular risk factors (Ism skriftserie Nr.28, 1993)(64). This health survey was conducted by the National Health Screening Service in cooperation with the University of Tromsø and local health authorities (65).

In Karasjok and Kautokeino, Figure I, 1723 individuals were invited to participate in the general health survey (Table I, Paper 1). 1347 persons (78.2%) attended the screening (66). A standard protocol, similar to that used in the

previous surveys of this population, was used (65;67). Those who attended the screening were given a questionnaire, to be filled out at home and returned by mail. It included questions concerning ethnicity (when two or more of the grandparents were Sámi, the subjects were defined as Sámi) and symptoms of pain and/or stiffness of the back (back pain of more than 4 weeks' duration and morning stiffness in the back) (Appendix). 1134 of 1347 participants (84.4%) identified themselves as Sámi, of whom 836 (73.7%), 424 men and 412 women, returned the questionnaire. Pain and/or stiffness of the back was reported by 210 persons (25.1%), who were classified as positive responders (Table II, Paper 1). Those who answered "no" to both questions regarding back complaints (548 subjects), or returned the questionnaire without answering the questions (78 subjects), were defined as negative responders. A non-responder was a person who did not return the questionnaire (299 subjects) (Figure 1).

All 210 positive responders were invited to a clinical examination, and 188 of them (89.5%) participated. Furthermore, a random sample of 206 persons among 626 negative respondents was invited to a clinical study, 160 of whom (78%) came to be examined (Paper 1).

The clinical examination took place first, followed by a blood test and radiographs on the same day. The clinical examination was carried out by the author, without knowledge of the HLA status or the results of the radiographic

examination. Measurements of lumbar flexion were done using the Schober test (68). A spondylometer was used to measure the total spinal mobility (69). Chest expansion was measured according to standard procedures (70).

HLA-B27 tissue typing was done for all of the 188 positive responders and for 160 negative responders who were clinically examined (Paper 1).

Colour Doppler echocardiography (CDE) was carried out on 188 (90%) of the back pain sufferers and 160 (78%) of the invited control subjects. None of these subjects had a previous diagnosis of AR. The methodology is described in detail in Paper 2.

The method used for the roentgenological examination and analysis is described in Papers 1 and 3. The effective total radiation dose for the lumbar column was approximately 1.6 milligray and for sacroiliac joints approximately 1 milligray.

The New York diagnostic criteria for definite AS were used, and only patients with definite radiographic changes in the sacroiliac (SI) joints were accepted as having definite AS (71). The grading system devised by Dale (72) for arthritic changes of the SI joint was used. In Dale's grading system, grade 0 refers to normal joints, grade 1 to suspicious changes, grade 2a to definite unilateral and 2b to definite bilateral changes, and grades 3 and 4 to severe arthritic changes.

Grade 5 is total bony ankylosis of the SI joints. In this grading system grades 2 and 3 represent definite arthritic changes and correspond to New York criteria grades 3 and 4 (Paper 1).

Table I. Modified New York criteria for AS

1. Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest
2. Limitation of motion of the lumbar spine in both the sagittal and frontal planes
3. Limitation of chest expansion relative to normal values corrected for age and sex
4. Bilateral sacroiliitis grades 2-4, or unilateral sacroiliitis grades 3-4 *

*Definite AS if the radiological criterion is associated with at least 1 clinical criterion.

Osteoarthritis was classified according to Kellgren and Lawrence (K/L) with a range from minor formation of entophytes on the joint margins (grade 1) to disintegration of the hip (grade 5)(73).

The Wiberg CE angle was defined as the angle formed by a line from the centre of the femoral head to the lateral margin of the acetabular roof, and a line

perpendicular to that joining the centres of the two femoral heads as described by Wiberg (47) (Paper 3).

AR was classified using the grading system devised by Gilbert J. Perry (74) (Paper 2).

Statistics: The statistical analysis was performed with SPSS v12.

Chi-square and t-tests were used as appropriate and P-values of less than 0.05 were considered to be statistically significant. All different statistical analyses used are described in detail under materials and methods for each paper.

Ethics: The study was approved by the Regional Ethical Committee for Medical Research in Northern Norway. The Data Inspectorate (Datatilsynet) gave us permission to establish personal records. This work was supported by the programme “Medisinsk forskning i Finnmark”, University of Tromsø.

7. Summary of the results

Paper 1

A population survey of the Sámi population of the municipalities of Karasjok and Kautokeino in northern Norway showed that the prevalence of ankylosing spondylitis was 1.8% according to the New York criteria. Eleven cases of ankylosing spondylitis were found, seven in men and four in women. Only four of the 11 people with observed cases of ankylosing spondylitis were aware of the diagnosis of ankylosing spondylitis prior to the survey. Ten of 11 patients with ankylosing spondylitis had the HLA-B27 antigen (non-weighted SE=91%), which is found in 24% of the general Sámi population in this area. It was calculated without weighting that 6.8% (PPV) of B27-positive persons had ankylosing spondylitis. The chance of a B27-positive person with back pain or stiffness having AS was 19.6%. But the weighted analysis revealed that only 73% of Sámi had the HLA-B27 antigen. Thus, the Sámi population has a high prevalence of AS and HLA-B27, but the association between the HLA-B27 gene and AS is weaker than among Caucasians.

Paper 2

The aim of this study was to estimate the prevalence of aortic regurgitation (AR) in the Sámi population and its association with ankylosing spondylitis and HLA-B27. Another aim was to complete a follow-up of all AR subjects at the screening.

The prevalence of AR was 8.8% in Sámi populations in northern Norway, which is comparable to that reported in other populations; however, data from other populations are sparse. Ankylosing spondylitis was strongly associated with AR, but not with the HLA-B27 antigen. The clinical follow-up programme 15-17 years later did not indicate considerable progression of low grade AR.

Paper 3

The overall aim of this study was to evaluate the acetabular coverage of the femoral head as measured by the centre-edge (CE) angle of Wiberg and to evaluate any association between low back pain and hip dysplasia in the Sámi population. High prevalence of hip dysplasia was found in this Sámi-dominant area. The CE angle of Wiberg was found to be 28 (+/-7) and 27 (+/-7) degrees for the left and right hips, respectively. 17% of the Sámi had definite dysplasia,

21% had light dysplasia and 62% had normal hip joints. Thus, 38% of the Sámi had more or less dysplastic hips. The oldest patients had significantly smaller CE angles than the younger ones. However, no association was found between acetabular dysplasia and back complaints.

Paper 4

The aim of this study was to investigate the relation between acetabular dysplasia of the hip and the risk of developing hip osteoarthritis in a Sámi population with a very high prevalence of acetabular dysplasia: 21-38%. A population-based survey was conducted in a core Sámi area in Norway. Of 836 responders from the general health survey, a total of 315 middle-aged subjects underwent clinical and radiological examinations. The results demonstrated that 6.8% of the Sámi population had hip osteoarthritis. The logistic regression analysis did not show a significant association between acetabular dysplasia and hip osteoarthritis. Only age had a statistically significant influence on osteoarthritis. There is no evidence for the influence of acetabular dysplasia on the development of hip osteoarthritis in this middle-aged Sámi population.

8. General discussion

8.1 Methodological considerations

This study is a cross-sectional population based only among the Sámi population in two municipalities in Finnmark, Norway (Karasjok and Kautokeino).

8.1.1 Sampling discussion

This study was primarily designed to estimate the prevalence rate of AS in a Sámi population in Norway, and to evaluate other clinical problems concerning AS on the basis of a population-based study. But even from the beginning we had plans to evaluate how ankylosing spondylitis influences the heart and also to evaluate Sámi hips, as a part of the same study. We wanted to discover the actual incidence of hip dysplasia among the Sámi, and to evaluate the association between acetabular dysplasia and hip OA.

Disproportionate stratified sampling of the entire population was used, by over-sampling the portion of the population who reported back problems in order to obtain a large enough number of AS patients to allow a separate analysis of adequate precision of AS subjects. The cases were then weighted to restore the original proportions. This weighting process generally reduces the precision benefits of stratified random sampling. Standard error estimates based on disproportionate stratified samples may be either more or less precise than those based on simple random samples.

The weighted calculations in this work were done in the following way: those with back problems were weighted with 1.12 (210/188) and healthy subjects with 3.91 (626/160) (Figure 1).

Our chosen study design was tailored to AS diagnostic purposes (Paper 1). The alternative would have been to examine all 836 Sámi responders, including with X-rays (Figure 1). But we believe that it would have been difficult to obtain permission from the ethical committee for such a study.

The study design may to some degree have been selected for purposes of AR diagnosis because of the over-sampling of the symptom-bearing group (back-pain group) of the population. On the other hand, we have tried to compensate for possible bias in the study design by using weighted calculations. It is worth noting that the prevalence of AR was not significantly different in the back-pain group as compared with the controls ($p=0.4$), and the non-weighted and weighted prevalence were almost the same: 8 and 8.8%, respectively (Paper 2).

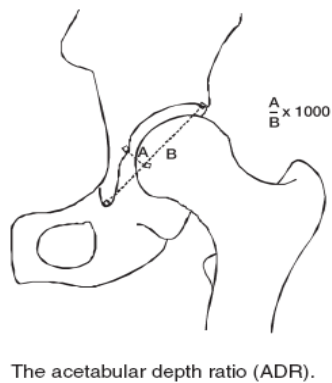
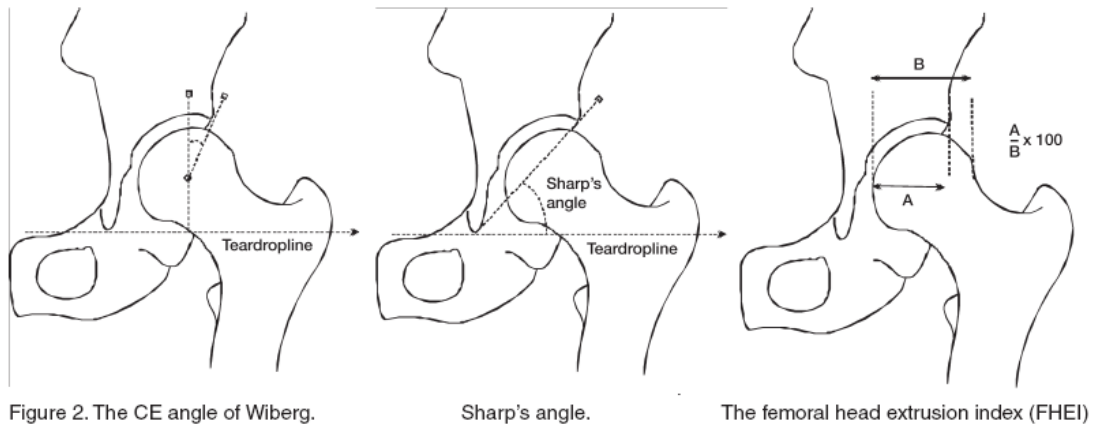
The same result was also obtained with regard to the hips. There was no difference between the mean CE angles of the hips on either the left or the right side in those with and without back complaints (Table III, Paper 3), nor in the linear regression analysis (Table IV, Paper 3). The logistic regression analysis

revealed almost the same results regardless of whether non-weighted or weighted analysis was used, resulting in our assumption that our sampling procedure was appropriate for its intended purpose. But the results presented in the regression analysis in Papers 2, 3 and 4 were, in the end, based on non-weighted analyses, because of the risk of exaggerating minor differences in this relatively small amount of material culled from only a small number of cases. Thus we conclude that the sampling procedure described in Papers 2, 3 and 4 was appropriate for its intended purpose, although not ideal.

Further, the male/female ratio among all 1723 subjects invited to participate the study was 1.17. The sex ratio among the 1347 including both Sámi and non-Sámi, and the 1135 Sámi who attended the screening was 1.02. The 836 responders had a sex ratio of 1.03. Among the positive responders the sex ratio was 1.23, while it was only 1.04 among the examined positive responders. Further, among 626 negative responders the sex ratio was 0.97 and only 0.79 among those 160 subjects from the random sample who were examined. This indicates that men failed to participate in the clinical part of this study to a greater extent than women did.

Standard anteroposterior pelvic radiography has been the primary source in epidemiologic studies of AD. Several indices and ratios have been developed to

describe the dysplastic hip. Some of these are complex and time-consuming to use and do not seem to have any advantage over simpler indices (75).



The acetabular anatomy can be assessed by following parameters shown in Figure 2 and defined as:

1. **Sharp's angle/acetabular angle (AA)= AE/teardrop line**
2. **Acetabular depth to width ratio (ADR)=AE/DB ratio**
3. **Centre-edge angle (CE)=EC/CF angle**
4. **Femoral head extrusion index (FHEI)=H/G+H**

According to Jacobsen et al. (76) assessment of AD is critically influenced by pelvic orientation during recording. They observed a significant effect of varying rotation and varying inclination/reclination on CE angle, Sharp's angle and ADR in a cadaver pelvis study, while FHEI was not significantly affected by rotation.

According to Anda et al., pelvic incline in standing and supine pelvic radiographs varies only insignificantly (77). Further, CE angle, ADR, Sharp's angle and FHEI are found to be significantly interrelated (76).

We chose the CE angle as a measure for AD, simply because this is the most widely used parameter and is easy to measure. But the CE angle also has some limitations, e.g. the true lateral acetabular margin can sometimes be difficult to identify in anteroposterior radiographs (76). Moreover, variations in pelvic orientation during recording will eventually have the same influence on subjects with or without AD, i.e. any errors will be the same in both groups, and therefore not influence the analyses.

The OA diagnosis is based on a combination of radiological evidence of joint degeneration, i.e. osteophytes, subchondral sclerosis, subchondral cysts and reduced joint space width, in combination with characteristic subjective symptoms.

We assessed OA with the widely-used classifications of Kellgren/Lawrence (K/L), ranging from minor formation of osteophytes on the joint margins (grade 1) to disintegration of the hip (73). One objection against this classification model has been the problematic reproducibility of readings (78). Several authors therefore use JSW as the primary criterion for hip OA, as it has been reported to have superior reproducibility, and is therefore especially recommended for use in epidemiological studies (79;80). However, at the time when we performed this study, the natural distribution of JSW had not been evaluated in asymptomatic subjects.

Jacobsen et al. (80) assessed the repeatability of readings of minimum JSW against repeated KL scores, and proved that the repeatability of KL is almost as good as JSW, when KL grade=2 or more, is defined as definite OA (kappa=0.82-0.85). Also, recently Reijman et al. (81) confirmed that the KL score of 2 or higher at the baseline is the strongest predictor of progression of hip OA, especially in people with hip pain at baseline, and concluded, “In a clinical situation and for clinical trials an X-ray has strong additional value to identify people who are at high risk for progression of hip osteoarthritis.” In our study we defined OA as being present when the KL score was 2 or higher. We conclude, therefore, that the KL score system which we used in this study was satisfactory.

We then evaluated the association between AD and radiologically-defined incidence of hip OA, and not the association to clinically-defined OA.

8.1.2 Validity: selection bias, information bias and confounding

Bias is a term for systematic error in a study giving an estimate which diverges from the true value of the population. This is different from the effects of random measurement errors which can be “eliminated” by increasing the sample size. There are three main groups of bias: selection bias, information bias and confounding.

Selection bias is a skewing of the results in a study because of inadequacies in the way subjects are selected for the study. The main reason for this is a high non-response rate, which is not the case in our study. The attendance rate was high in this study, 74% (Tables I and II, Paper 1). Women attended the screening to a greater degree than men, which may have influenced the results to some degree, especially for diagnoses of AS and AR, because both are male-dominant diseases, according to the literature. Prevalence estimation is influenced to a greater degree by selection bias than are association measurements, e.g. an odds ratio. In cross-sectional population studies only the survivors are examined. The diseases we have studied, AS, AR, AD and hip OA, do not have especially high mortality rates, and therefore we do not believe that this type of bias has influenced the conclusions.

Information bias is a systematic skewing of the results because information about exposure and diagnosis vary systematically. In our study incorrect classifications are unlikely because we consistently used accepted diagnosis criteria, and few people were involved in the evaluation of the subjects. For example, one person carried out all the clinical and echocardiography examinations, one radiographer carried out all the radiological examinations, one investigator (orthopaedist) interpreted all the hip X-rays (Papers 3 and 4) and two investigators (radiologists) interpreted the back X-rays (Paper 1). This study was performed at a time when it was least popular to be a Sàmi. The self reported ethnic identity were probably lower than the true for the Sàmi on that time, without biasing our results, because our analyses were done only among Sàmi.

Confounding means that the observed association actually represents an association between another variable and the endpoint. This can occur if there is a strong association between the measured variable and a confounding factor which is poorly measured or not included in the study at all. Our data were stratified in multivariate analyses, and no confounding was detected.

Unfortunately, we did not have access to the subject populations` biometrical data (height and weight). Thus we did not include these variables in the final analysis.

8.2. Results

Our population-based study revealed a total prevalence of AS of 1.8% in the Sámi population, with 24% of the population being HLA-B27 positive. Our study is currently the only population study conducted with controls from among the symptom-free members of the population in which the symptom-free persons were also X-rayed. We found 5.3% (10 AS cases/188) AS among those who reported back pain and/or stiffness and 0.6% (1 AS case/160) among the symptom-free portion of the population, i.e. nine times more disease in the symptom-bearing group of the population. If our study had been conducted as another similar study had been (82;83), with the assumption that the symptom-free portion of the population did not have AS, our prevalence would have been 1.3%, i.e. the same result as in Gran's study from 1985 (82). To establish a correct diagnosis, accepted diagnostic criteria for AS were used: the New York diagnostic criteria for AS (84), Table I.

The reported prevalence of AS from population surveys varies greatly, from 0.1% in the Netherlands to 6.2% among male Haida natives of Canada (2;85). The HLA-B27 frequency was 7.8% and 50%, respectively. Gran's survey of Caucasians from Tromsø, northern Norway, revealed a prevalence from 1.1 to 1.4% in a population with an HLA-B27 prevalence of 16%. (82). We believe that the significant reported differences in the prevalence of AS stem primarily from differences in study design. Most prevalence-based studies in the world are

not based upon population studies, due to the difficulty inherent in carrying out such studies.

We believe that the study design we used was ideal as a means of finding the minimum prevalence in the population. Since AS is a male-dominant disease, and a larger percentage of males than females fail to attend screenings, as discussed above, we may have missed some cases, which means that our results are a minimum estimate for AS (Paper 1). The only possibility over-diagnosing AS in this study was on the level of radiograph interpretation. All films were independently read by two experienced radiologists who were unaware of the clinical and HLA status of the subjects; however, they were aware of the fact that all the films were from this survey. The degree of interobserver variation was acceptable as shown in earlier surveys (72).

The distribution of HLA-B27 varies considerably in different populations: 50% of Haida natives in Canada (6), 24-26% of Sámi (1;66), 14-17% of non-Sámi in Northern Scandinavia and Finland (5), 6-8% of Caucasians in central Europe and North America, about 2% of Chinese and African-Americans, and only 0.2% of Japanese have these genes (7;86). But the relation between HLA-B27 and AS (>90%) has previously been estimated as equally strong in different studies, at least among Caucasians (4). A recent study from Turkey showed that HLA-B27 was found in only 70% of AS patients (13).

Ten of our 11 AS patients (91%) were HLA-B27 positive, which is compatible with the above-mentioned theory. However, our weighted analysis found that only 11 out of 15 (73%) AS subjects were HLA positive. Thus, the weighted analysis of HLA-B27 and AS (unpublished, but calculated from the own material) showed a SE, SP, NPV, PPV and AC for HLA-B27 of 73, 78, 99, 5.6, and 78%, respectively; i.e. only 73% of all AS subjects were estimated to be HLA-B27 positive, in a population with a weighted prevalence of 1.8% (Table II).

If we had assumed, as others have (82;83), that the non-back-pain group was free of AS, the same procedure would have revealed an AS prevalence of 1.3%, a SE and NPV of 100% and a PPV of 9.4% for HLA-B27 among those 836 responders. The frequency of HLA-B27 among AS subjects would then have been 100%. The high sensitivity among those subjects with back complaints affords little chance of missing AS diagnoses.

Our weighted analysis revealed a sensitivity of 73% of HLA-B27, which is comparable with the results of a recent Turkish study (70%) (13), although the Turkish study design was quite different from ours. There is no doubt as to the association between AS and HLA-B27. But the strength of this association is more unclear than assumed previously, in any case in population-based studies. Our weighted study, like the Turkish study and a Greek study (80%), reveals a

lower association than in earlier reported studies (13;14). This is also supported by a study from West Africa, where the prevalence of HLA-B27 was 6%, but the prevalence of AS was 0% (15). All these studies indicate that HLA association varies in strength among different ethnic groups. These findings may indicate that different genetic and environmental factors are involved in the pathogenesis of AS as described by Breban (87).

Table II

Weighted HLA-B27 * AS Crosstabulation of Sámi responders (NO:836)

HLA-B27	AS		Total	
	No	Yes		
No	637	4	641	NPV 99.4%
Yes	184	11	195	PPV 5.6%
Total	821	15	836	AC 77.6%

SP 78%

SE73%

AS= ankylosing spondylitis

Why some population groups, especially in Arctic areas, have such a high frequency of HLA-B27 is unknown. It has been speculated that the presence of this gene was an advantage, increasing resistance to specific infections such as tuberculosis and leprosy (6). If this gene were protective, then after such epidemics the HLA frequency in the population would increase. But this could just as well apply to other epidemic diseases. It is known that the Spanish influenza pandemic hit Finnmark very hard in the autumn of 1918 (88). Mamelund demonstrated a high morbidity and mortality rate for Spanish influenza in municipalities with a large percentage of Sámi. The areas that were hardest hit were Alta, Karasjok and Kautokeino, where more than 90% of the population at that time was Sámi (89). The mortality rate in these municipalities was four times higher than in the rest of the country, where it was 1-1.3%. The pandemic probably introduced a new virus that few, if any, had the immunity to fight. Karasjok and Kautokeino were very isolated communities at that time, with a low rate of immigration. I have been told by older people that the influenza epidemic started with a high fever and arthralgia, followed a few days later by severe diarrhoea, resulting in many deaths due to dehydration. Perhaps HLA-B27 provided some kind of protection against the secondary severe and complicated infections.

Because of the known association between AS and HLA-B27, AS and AR (19;90), it was of great interest for us to also perform a CDE examination of all

included subjects, and to include all AR subjects in a clinical follow-up programme (Paper 2).

The weighted prevalence of previously undiagnosed AR was 8.8% in this generally young and middle-aged population (20-64 years). Our study reveals that AR increases with age, which is compatible with earlier CDE studies (91;92).

Logistic regression analysis detected only a significant effect of AS and age on AR, with odds ratios of 7.4 and 2.1, respectively. The HLA-B27 antigen was not associated with AR (Paper 2). The clinical follow-up programme 14-17 years later gave no indications for rapid progression of low-grade AR (Paper 2).

The previously reported prevalence rates of AR have varied from 0% to 33% (92-95). These results were based on small groups of healthy volunteers.

From 1999 until the present, to our knowledge only five papers have been published concerning the prevalence of AR in a general population (96-100). In all these studies AR is independently associated with age, but only two of these studies reveal a sex association, with male dominance (96;98). The other three studies are gender-neutral. Our study demonstrated a female dominance of AR, which other studies have not shown, which may be explained by the selection

bias that results from the fact that more males than females fail to participate in screening.

In 1918, Wessel reported a high prevalence of DDH as compared to the Western European population in general (23). In Paper 3 we map the acetabular coverage of the femoral head as measured by the centre-edge (CE) angle of Wiberg. We also evaluate the possible association between low back pain, hip OA and hip dysplasia. A high prevalence of AD was found in this Sámi-dominated area in northern Norway: 17% had definite dysplasia and 21% had light dysplasia. Thus, 38% had more or less dysplastic hips. The oldest subjects had significantly smaller CE angles than younger persons, but no association was found between acetabular dysplasia and back complaints. Our study revealed that the CE angles of the Sámi population were far smaller than in other populations.

In the last paper (Paper 4) we investigate the relation between AD and the risk of developing hip OA in this very high-prevalence population of AD.

Conflicting results have been published concerning this question, which is discussed in detail in Paper 4. Since the work of Wiberg (47) it has been assumed an aetiological relationship between DDH and hip OA. This theory is supported from radiographic observations in patients with hip OA (48), and from a cross-sectional study from Denmark (56), revealing a weak, but

significant association between AD and hip OA. But two cross-sectional studies, similar to our study, could not show any association between these disorders (29;32). Only two prospective studies (58;81), seems to prove that AD is a risk factor for hip OA in elderly patients. Lane (58) revealed a modestly increased risk in elderly white women(> 65 years of age by including, mean follow-up 8 years), while Reijman (81) revealed strong independent risk among both sexes (>55 years of age by including, mean follow-up 6.6 years). Our study with a mean age of 48 years could not confirm any aetiological association between AD and hip OA (OR=0.99, 95% CI 0.92-1.03). The risk of type 2 error seems therefore to be small because of narrow CI (Paper 4, Table III).

Therefore, other factors may be important in the development of hip OA, including hereditary, ethnic and other as yet unknown factors, for instance the possibility that OA is an infectious disease.

8.3. Conclusion

1. We confirm the previously demonstrated high prevalence of human leukocyte antigen HLA-B27 (24%) and demonstrated a very high prevalence of ankylosing spondylitis (1.8%) among the Sámi in Finnmark. Only 36% of the ankylosing spondylitis patients were aware of their diagnosis prior to the survey. The study confirms a strong association between ankylosing spondylitis and HLA-B27

(73%), but also indicates that the association is weaker among the Sámi than among Caucasians (>90%).

2. The symptom-free aortic regurgitation has a relatively high rate of occurrence (8.8%) in the Sami population, and that aortic regurgitation is associated with age and AS, but not with HLA-B27. During the follow-up period of 15-17 years for low-grade aortic regurgitation, almost no progression was found.

3. A high prevalence of hip dysplasia of the Sami population in Finnmark was found as 38% had more or less dysplastic hips. However, we found no strong associations between hip dysplasia and HLA-B27, back pain or hip osteoarthritis. The prevalence of hip osteoarthritis in this middle-aged sample of the Sámi population (20-64 years old) was not especially high (6.8%), and is comparable to that of other population groups.

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