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ORIGINAL RESEARCH

The Northern Swedish Population Health Study (NSPHS) – a paradigmatic study in a rural population combining community health and basic research

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ABSTRACT

Introduction: Health care and research in rural populations are often limited due to poor infrastructure and small sample sizes. However, such populations have a need for medical care and can be of great value when studying the health effects of lifestyle and genetic factors. The Northern Sweden Population Health Study (NSPHS) is a paradigmatic study that combines a survey of the health status and specific needs of the community with basic research into the environmental and genetic determinants of non-communicable diseases. This article presents the NSPHS results on lifestyle, subclinical, and clinical measures and gives a review of the past contributions of this study to our understanding of the genetic determinants of disease in international collaborations.

Methods: A population-representative, cross-sectional sample (n=656) was examined from the Karesuando parish in Northern Sweden north of the Arctic Circle. The population consists of individuals living a traditional, subsistence-based lifestyle (TLS, n=96), mainly based on reindeer herding, hunting and fishing, and others following a modern, more industrialized lifestyle (MLS, n=560), similar to other western European countries. Subgroups with a modern versus traditional lifestyle were compared separately in men and women, highlighting differences in lifestyle (eg diet, physical activity), subclinical (eg blood circulation, blood lipids, lung function) and clinical measures (eg disorders of the cardiovascular, metabolic, and musculoskeletal system).

Results: TLS men and women consumed much more game meat (Men: 71 vs 194 g/day, p=0.0011; Women: 56 vs 140 g/day, p=0.0020) and less non-game meat (Men: 88 vs 42 g/day, $p=1.4\times10^{-7}$; Women: 81 vs 42 g/day, p=0.026) compared with the respective MLS group. TLS men consumed less milk ($p=4.2\times10^{-4}$), and TLS women less vegetables (p=0.042). TLS men reported more physical activity at work (p=0.042) and TLS women less physical activity at leisure (p=0.0023). Total cholesterol (Men: 220

vs 244 mg/dl, p=0.0031; Women: 225 vs 246 mg/dl, (p=0.049) and LDL cholesterol levels (Men: 134 vs 153 mg/dl, p=0.012; Women: 133 vs 146 mg/dl, p>0.05) were higher in the blood serum of TLS men and women than in the MLS comparison group. While TLS women showed a higher rate of myocardial infarction (5% vs 16%, p=0.024), TLS men reported a dramatically higher frequency of body pain consistently, for example in the lower back (0% vs 25%; p>0.05).

Conclusions: A consistent pattern was found of differences between individuals living a traditional versus modern lifestyle and between the sexes, identifying specific health risks for each group. Women with a traditional lifestyle were exposed to a greater risk for cardiovascular disease (especially myocardial infarction) and men with a traditional lifestyle reported higher rates of orthopedic symptoms (eg body pain). We also show that studies of rural populations can make a substantial contribution to basic research into understanding the environmental and genetic determinants of disease. The European Special Populations Research Network (EUROSPAN) provided an excellent example of a platform combining studies of rural populations from different parts of Europe that can leverage these for collaboration with large international consortia.

Key words: cardiovascular disease, community health, disease indicators, genetics, lifestyle, Northern Sweden, orthopedic disease, rural population.

Introduction

Health care and research in rural populations are often limited due to a lack of infrastructure and small sample sizes[1]. Nonetheless, such populations have a need for medical care and can be of great value when studying the health effects of lifestyle and genetic factors. For example, the northern parts of Norway, Sweden, Finland and the Kola Peninsula (collectively called the Northern Shield) are affected by both climate and cultural changes. These cause a transition from a traditional, subsistence-based lifestyle to a modern, industrialized lifestyle for many local people[2] Their traditional lifestyle is based on reindeer herding, fishing, and hunting, but an increasing number of people now have other occupations and, therefore, have other diet and activity levels[3]. The effect of this transition on disease prevalence is at present unknown and requires special medical attention[4]. Therefore, there is a need to focus on the health conditions of rural populations on the northern periphery of major continental areas.

At the same time as rural populations in Nordic regions undergo lifestyle changes, many common diseases are spreading with epidemic proportions in most urban populations with a modern, industrialized lifestyle[5]. Although major international efforts are underway to identify environmental and genetic factors relevant to disease development by establishing very large prospective cohorts in metropolitan populations[6,7], a major difficulty lies in the complexity of the environmental and genetic factors relevant for common disease. Because this complexity is typically reduced in rural compared with urban populations (Table 1), studies of such populations have a higher potential for determining risk factors related to common disease than urban populations[8-12].

Variation in environmental factors, for example climate or diet, is typically reduced in rural relative to urban populations[8]. If risk factors for medical traits are examined, these homogenous conditions create a natural study design controlling other influences and reducing the 'noise' (confounders) compared with the 'signal' (risk factor)[13]. A second consideration is that lifestyles between rural and urban populations can be very different[14]. This will maximize the health effects of lifestyle factors in comparative studies making them easier to detect. In addition, rural individuals usually live in the same environment over an extended time period, which again increases the health effects of their lifestyle. If a subgroup within a rural population is changing towards a modern, industrialized lifestyle, the health effects of lifestyles differences can even be compared within the same population. If the lifestyle differences are known and measured, advantage can be taken of similar environmental conditions to control noise and include known environmental differences in the analytical model. This way one can again remove the noise and strengthen the signal. In addition, the effect of the measured environmental confounders and its interactive effects on the examined medical trait can be studied[13].

Table 1: Characteristics of traditional versus modern lifestyles: examples comparing a traditional lifestyle in Northern Sweden with a modern lifestyle in Western Europe

Traditional lifestyle† in rural areas: example, traditional lifestyle in Northern Sweden	Modern lifestyle† in urban areas: example, modern lifestyle in Western Europe
History related to a specific geographic area Example: district in Northern Sweden, little migration	History unrelated to a specific geographic area Example: migration between cities, countries, continents
Extreme climates, ecological niches Example: coldness, snow, ice, little vegetation	Moderate climate, ecological variety Example: mild seasons, plenty vegetation
Rural, local, low-quality infrastructure Example: small villages, long distances, little public transport	Urban, central, high-quality infrastructure Example: big cities, short distances, good public transport
Subsistence Example: people consume their own products	Abundance Example: people sell most of their products
Local food sources Example: reindeer, moose, berries, mushrooms	Global food sources Example: beef, pork, fruits from abroad
High physical activity Example: hiking, riding, tending herds	Low physical activity Example: office work, motorized transport
Manual production Example: manual work, work animals	Industrialized production Example: computers, robots, machines
Low environmental impact Example: small population size, recycling, organic materials	High environmental impact Example: large population size, waste, inorganic materials
Cultural homogeneity within population Example: local foods and traditional clothes	Cultural heterogeneity within population Example: international foods and various styles of clothes
Cultural heterogeneity between populations Example: different local foods and traditional clothes	Cultural homogeneity between populations Example: same international foods and styles of clothes
Genetic homogeneity Example: higher frequency of marriages within an ethnic group	Genetic heterogeneity Example: higher frequency of marriages between ethnic groups

†The features described are stereotypes which do not take account of exceptions.

The history and structure of a population also influence the power of mapping genetic factors relevant for disease development. Many rural populations have lived isolated from surrounding populations while either retaining a small and stable population size over a long time, experiencing a recent population bottleneck followed by exponential growth, and/or showing a higher level of consanguinity. All these factors result in lower heterozygosity[15], which reduces the overall genomic variation and increases the frequency of rare disease-relevant genotypes[16]. For example, genes that cause rare monogenic genetic bone diseases (eg osteopetrosis and sclerosteosis), which now represent important molecular targets for the design of new drugs to treat osteoporosis[17], were identified in a rural population.

The Northern Sweden Population Health Study (NSPHS) was initiated to provide a health survey of the population in this area and to study the medical consequences of lifestyle and genetics. This article will provide the results on differences between modern and traditionally living individuals regarding lifestyle, subclinical, and clinical measures within the NSPHS study. In the discussion, some of the contributions of this project to past publications of the European Special Populations Research Network (EUROSPAN, http://www.eurospan.org) and other international consortia, which discovered novel genetic determinants on medical traits[18-28], will be reviewed.

Methods

Organization

Data collection in a rural population requires special consideration of specific geographical, cultural, and historical conditions beyond usual scientific standards. Therefore, supporting material regarding features of the study the authors found to be important are provided (Appendix I) for the benefit of other researchers planning similar research.

Sample

The study population has been living remote from other influences for a long time due to geographical, historical, political, cultural, and linguistic reasons. Therefore, the population showed closer family relationships than urban populations, and had a genealogy that was well documented in church records, extending up to 300 years. According to the Sweden Census, on 31 December 2006 this parish had 1071 inhabitants of whom 826 (77%) were aged 15 years or older (and therefore eligible for this study). Overall, 740 (90%) of 826 eligible individuals gave a written informed consent. Of the 740 participants of the study, 656 subjects (89%) contributed complete data, resulting in a final sample consisting of 347 (53%) women and 95 (14.5%) individuals with a traditional lifestyle.

The NSPHS study was approved by the local ethics committee at the University of Uppsala (Regionala Etikprövningsnämnden, Uppsala, Dnr 2005:325) in compliance with the Declaration of Helsinki[29]. All participants gave their written informed consent to the study. For participants of under legal age, a legal guardian also signed. The procedure used to obtain informed consent and the respective informed consent form has been recently discussed according to current ethical guidelines[30].

Measures

The study included a comprehensive collection of data on genealogy, sociodemography, body size, blood samples for clinical chemistry, medical history of participants and family members, and lifestyle. The following describes only measures with relevance to cardiovascular, metabolic, and orthopedic disease.

Genealogy, sociodemography, and body size: Assessed were genealogy, sociodemography (eg sex, age, occupation) and body size measures (eg height, weight, hip circumference, and body mass index). Individuals were grouped into 4 groups based on self-reported information on sex and occupation, distinguishing individuals reporting reindeer herding as their major occupation versus all other occupations. Individuals reporting reindeer herding as their major occupation performed related activities (eg tending herds, processing reindeer meat and fur, buying and selling reindeer or reindeer products) on a regular, daily basis, and showed other lifestyle characteristics, for example high mobility and seasonality of work. Unclear cases were discussed with the district nurse who knew most of the community members and their families. These four subgroups with different sex and occupations/lifestyles are referred to as: traditional lifestyle (TLS) men, TLS women, modern lifestyle (MLS) men, and MLS women.

Lifestyle:

Diet Data were collected with a food frequency questionnaire based on the Northern Sweden 84-item Food Frequency Questionnaire (NoS-84-FFQ). This food frequency questionnaire was developed, validated, and applied within the Västerbotten Intervention Program[31-33]. The answer options were in an 11 point format: 0='Never', 1='less than 1 time per month', 2='1 to 3 times per month', 3='1 time per week', 4='2 to 4 times per week', 5='5 to 6 times per week', 6='1 time per day', 7='2 to 3 times per day', 8='4 to 5 times per day', 9='6 to 8 times per day', 10='9 to 10 times per day'. For each food item, daily intake was calculated in grams per day as a standardized unit of measurement and the items aggregated to food categories, such as game meat, non-game meat, fish, dairy products, vegetables, or fruit. Food intake was converted to nutrients (eg fibre, carbohydrates, protein, fat, and alcohol) and their energy equivalent using the food database of the Swedish Food Administration[34].

Included in the questionnaire were several items on foods specific for the lifestyle in this geographic region, in particular on game consumption (reindeer, moose). The construct validity (known-groups validity) of the items on game consumption added to the NoS-84-FFQ questionnaire was evaluated. Traditional (n=94) versus modern lifestyle (n=505) individuals were compared. A highly significant, large effect size (ES) in men ($ES=(M_{TLS}-M_{MLS})/SD_{pooled}=1.25$, $p=9.7\times10^{-04}$) and women ($ES=1.15$, $p=2.9\text{x}10^{-05}$) was observed in the expected direction, corresponding to an approximately three times higher consumption of absolute overall game intake in those with a traditional lifestyle.

Physical activity Two self-report scales were used to measure overall physical activity at work and at leisure. The Work Activity Scale (WAS, 6 items) addressed typical occupational physical activities: sitting, standing, walking, lifting, and general indicators of physical activity, that is sweating and tiredness after work. The Leisure Activity Scale (LAS, 4 items) asked for various typical free-time activities, such as walking, cycling, other sporting activities, and sweating as a general indicator of physical activity. Participants reported the frequency of each activity on a 5 point rating scale (1='never', 2='seldom', 3='sometimes', 4='often', and 5='always'). Both scales showed satisfying internal consistency with Cronbach's α(WAS)=0.73 and Cronbach's α(LAS)=0.70.

Other health risks: Participants were asked about their consumption of cigarettes and snuff (a regional form of tobacco consumption where tobacco infusion is retained in the mouth) and whether they had ever experienced a work or traffic accident. Answers were given in a dichotomous format (0='no', 1='yes').

Subclinical measures

Blood measures: Resting pulse rate and systolic and diastolic blood pressure were measured. Total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in the blood serum were quantified by enzymatic photometric assays using an ADVIA1650 clinical chemistry analyzer (Siemens Healthcare Diagnostics GmbH; Eschborn, Germany) at the Institute for Clinical Chemistry and Laboratory Medicine, Regensburg University Medical Center, Germany. Sphingolipids and phospholipids in the blood plasma were quantified by electrospray ionization tandem mass spectrometry (ESI-MS/MS) in positive ion mode as described previously[35-37].

Lung function: Spirometry was performed in a sitting position without noseclips using a Spida 5 spirometer (MicroMedical; http://www.medisave.co.uk). Three consecutive lung function measurements per participant were performed and the maximum value per measured lung function parameter was used for further analysis. Within the scope of this article, Peak Expiratory Flow (PEF), Forced Expiratory Volume (FEV), and Forced Vital Capacitiy (FVC) were analyzed.

Bone mineral density: Bone status was assessed at the heel using the Lunar Achilles Express ultrasonometer (GE Healthcare; http://www.gehealthcare.com). Data are presented on the stiffness index as a Z-scaled measure of bone mineral density.

Clinical measures

Participants were asked during a clinical interview whether they suffered from symptoms or diseases of the cardiovascular, metabolic system or musculoskeletal system (eg pain during the last week) at present or had in the past (Table 5). The district nurse coded the reported symptoms and diseases in the relevant categories and asked for additional information if the self-report was unclear.

Statistical analysis

Primarily descriptive, comparative results are presented for relevant subgroups in the sample (Men: modern vs traditional lifestyle; Women: modern vs traditional lifestyle). Sample size independent effect size measures were calculated to evaluate the strength of the effects for quantitative ($ES_{quantitative}=(M_{TLS}-M_{MLS})/SD_{pooled}$) and binary ($ES_{binary}=Percentage_{TLS}-Percentage_{MLS}$) traits. According to a rule of thumb, $ES_{quantitative}$ values of approximately 0.2 were considered small, approximately 0.5 medium, and approximately 0.8 as large[38].

Also provided are inferential results per outcome. However, the authors are aware of the limited power of this sample and study design for hypothesis testing. Therefore, it is stressed that a lack of statistical significance does not prove that there is no relevant difference between the subgroups[39].

Nominal statistical significance was based on a local type I error of α=0.05; α inflation caused by multiple testing was not allowed for because conventional approaches are biased if applied to correlated outcomes (eg diet, activity, foods, lipids), as in this case. Instead this issue was addressed by reporting all conducted statistical tests[40], leaving the overall evaluation of statistical significance to the reader.

Because the data originates from a pedigree-based sample, adjustments for correlated data were made to derive the correct statistical inference[41]. A pedigree-based sample consists of individuals from a population where a substantial number of persons belong to the same extended families. This means that many participants are related to each other to varying degrees, but much closer than a sample from a general population-based sample. Therefore, a generalized linear mixed effects model was applied to estimate the effect of lifestyle on various outcomes in the male and female subsample. Deviations from normality of quantitative traits (eg body measures, diet, physical activity, and lipid levels) were corrected by inverse-normal transformation. Binary outcomes remained untransformed. The analysis was performed using the statistical analysis system *R* (V2.8.1)[42].

Results

Body measures

Participants were compared according to traditional (n=95) and modern (n=559) lifestyle separately in men (n=308) and women (n=346), regarding body size, subclinical, and clinical measures. TLS men were on average 4 years older (p=0.021) and TLS women on average 12 years older (p=0.0022) than the corresponding MLS groups. There were no substantial mean differences in weight for men and women, but TLS women were on average 6.8 cm shorter (p=0.0013), resulting also in a 2 kg/m^2 higher Body Mass Index (p=0.022) for TLS women (Table 2).

Lifestyle

Diet: Men and women with a traditional lifestyle consumed on average approximately 50% less non-game meat (Men: 87.95 vs 42.03 g/day, $p=1.4\times10^{-07}$; Women: 81.03 vs 42.06 g/day, p=0.026) and milk products (Men: 581.22 vs 298.93 g/day, p=0.0011; Women: 430.83 vs 360.15 g/day, p>0.05) compared with those with a modern lifestyle. However, TLS men (71.02 vs 193.63 g/day, p=0.0011) and women (56.42 g/day vs 139.92 g/day, p=0.0020) consumed approximately 3 times more game meat than MLS subjects. Participants with a traditional lifestyle consumed less vegetables (Men: 59.05 vs 53.17 g/day; p>0.05; Women: 100.00 vs 71.77 g/day, p=0.042), but their intake of fruit (including berries) was higher, although these differences did not reach nominal significance (Table 3).

Among the macronutrients, fat (Men: 65.24 vs 58.49 g/day, p=0.035; Women: 57.52 vs 51.31 g/day, p>0.05) and alcohol intake (Men: 1.55 vs 0.94 g/day, p>0.05; Women: 0.83 vs 0.22, p=0.0044) were both substantially lower in TLS subjects. Intake of protein was higher in TLS men and women, although this difference was not significant. The total energy intake based on self-reported food intake was higher in TLS men and lower in TLS women, which corresponds to self-reported physical activity at work (all p>0.05, Table 3).

Table 2: Body measures in modern living men and women and those living traditionally

Measure	Men				Women			
	Modern (*n*=251) *M*(*SD*)	Traditional (*n*=57) *M*(*SD*)	*ES*	*p*	Modern (*n*=308) *M*(*SD*)	Traditional (*n*=38) *M*(*SD*)	*ES*	*p*
Age (years)	46.78 (21.70)	50.95 (16.47)	+0.20	2.13E-02*	45.18 (20.84)	56.84 (15.43)	+0.58	2.22E-03***
Weight (kg)	79.34 (14.94)	74.37 (12.71)	-0.34	9.99E-01	65.07 (13.40)	64.32 (10.65)	-0.06	4.12E-01
Height (cm)	172.31 (6.73)	165.82 (8.31)	-0.92	5.32E-02	159.23 (6.66)	152.42 (6.48)	-1.02	1.34E-03**
Hip Size (cm)	99.66 (15.41)	97.04 (8.56)	-0.18	5.56E-01	93.21 (13.18)	96.84 (11.31)	+0.28	8.65E-02
BMI (kg/m^2)	26.71 (4.77)	26.92 (3.35)	+0.05	2.00E-01	25.75 (5.13)	27.67 (4.23)	+0.38	2.20E-02*

Quantitative traits were rank-normal transformed for statistical testing.
ES, Effect size = $(M_{TLS} - M_{MLS}) / SD_{pooled}$
**p*=]0.01; 0.05]=[1.00E-02; 5.00E-02]; ** *p*=]0.001;0.01]=]1.00E-03;1.00E-02]; ****p*=[0.00;0.001]=[0.00;1.00E-03].

Other health-related behavior: Smoking and using snuff showed minor variations between lifestyles, apart from smoking which was more frequent in traditionally than modern living women (12.34% vs 23.68%, all *p*>0.05, Table 3).

TLS men showed increased physical activity at work (*p*=0.042) but decreased activity at leisure (*p*=0.0057) compared with MLS men. TLS women, however, reported similar, but lower physical activity at work (*p*>0.05) and substantially less activity in their free time (*p*=0.0023, Table 3).

TLS men showed a dramatically higher frequency of working accidents (0.45% vs 37.50%) and traffic accidents (0.45% vs 40.00%) compared with MLS men. Traditionally living women had similar rates of work accidents (3.45% vs 0.37%) but much lower rates of traffic accidents (19.33% vs 3.45%, all *p*>0.05, Table 3).

Subclinical measures

Blood circulation: Pulse rates of TLS participants were moderately higher in men (71.89 vs 74.28 bpm) and women (71.95 vs 74.62 bpm). Blood pressure levels were similar among men, but systolic (120.08 vs 124.74 mmHg) and diastolic (72.93 vs 73.95 mmHg) values tended to be higher in TLS women (all *p*>0.05, Table 4).

Blood lipids: Substantially elevated cholesterol levels (TC, LDL-C, and HDL-C) were found in male and female TLS participants. The differences for TC (Men: 220.43 vs 244.40 mg/dl, *p*=0.0031; Women: 225.11 vs 246.29 mg/dl, *p*=0.049) and LDL-C (Men: 134.36 vs 152.84 mg/dl, *p*=0.012; Women: 133.19 vs 146.21 mg/dl, *p*=ns) and HDL-C (Men: 54.83 vs 63.04 mg/dl, *p*=0.0042; Women: 66.56 vs 68.76 mg/dl, *p*>0.05) were of small to medium size. However mean total cholesterol levels of male and female MLS subjects were 220 and 225 mg/dl, respectively, which indicated a borderline high cardiovascular risk; and total cholesterol levels of TLS males and females were 244 mg/dl (men) and 246 mg/dl (women) on average, suggesting high risk[43]. On an individual level, this implied that among MLS participants 34% (195 of 561) fell into the high risk group, while 63% (61 of 97) of TLS subjects were exposed to a similar degree. Triglyceride levels also showed small differences between MLS and TLS men (232.28 vs 202.93 mg/dl) and women (166.72 vs 188.16 mg/dl), without reaching statistical significance (Table 4).

Table 3: Self-reported lifestyle in modern living men and women and those living traditionally

Lifestyle factor	Men				Women			
	Modern (*n*=251)	Traditional (*n*=57)	*ES*	*p*	Modern (*n*=308)	Traditional (*n*=38)	*ES*	*p*
Food Intake - *M*(*SD*)								
Meat, non-game (g/day)	87.95 (62.22)	42.03 (54.68)	-0.76	1.40E-07***	81.03 (74.23)	42.06 (35.18)	-0.55	2.56E-02*
Meat, game (g/day)	71.02 (151.07)	193.63 (181.99)	+0.78	1.13E-03**	56.42 (62.39)	139.92 (93.00)	+1.26	1.95E-03**
Meat, fish (g/day)	23.26 (25.56)	18.25 (19.13)	-0.21	2.27E-01	23.54 (25.64)	18.33 (20.94)	-0.21	1.27E-01
Milk products (g/day)	581.22 (490.00)	298.93 (294.73)	-0.62	4.19E-04***	430.83 (415.23)	360.15 (276.96)	-0.18	2.92E-01
Eggs (g/day)	5.84 (7.09)	4.53 (4.66)	-0.20	1.91E-01	6.22 (8.08)	5.90 (8.66)	-0.04	3.33E-01
Vegetables (g/day)	59.05 (58.30)	53.17 (59.68)	-0.10	1.70E-01	100.00 (121.69)	71.77 (53.24)	-0.24	4.2E-02*
Fruit (g/day)	154.00 (129.39)	208.98 (168.83)	+0.40	1.50E-01	265.42 (238.55)	284.80 (207.61)	+0.08	2.88E-01
Nutrient Intake - *M(SD)*								
Fibre (g/day)	17.33 (8.35)	20.11 (14.95)	+0.28	1.76E-01	23.17 (13.20)	22.79 (10.94)	-0.03	2.07E-01
Carbohydrates (g/day)	225.05 (100.16)	237.50 (210.52)	+0.10	1.58E-01	249.83 (128.62)	241.99 (141.92)	-0.06	1.79E-01
Protein (g/day)	91.97 (57.91)	112.31 (83.66)	+0.32	2.75E-01	88.21 (39.24)	96.55 (38.17)	+0.21	2.31E-01
Fat (g/day)	65.24 (32.23)	58.49 (31.66)	-0.21	3.53E-02*	57.52 (25.33)	51.31 (23.02)	-0.25	1.20E-01
Alcohol (g/day)	1.55 (2.41)	0.94 (1.52)	-0.27	4.18E-01	0.83 (1.68)	0.22 (0.52)	-0.38	4.41E-03**
Energy (kJ/day)	7991.43 (3355.45)	8301.49 (5841.95)	+0.08	1.67E-01	8088.77 (3406.61)	7845.45 (3512.83)	-0.07	2.52E-01
Tobacco Use - *n* (%)								
Smoker	34 (13.55)	10 (17.54)	+3.99%	9.99E-01	38 (12.34)	9 (23.68)	+11.34%	9.99E-01
Snuff user	93 (37.05)	20 (35.09)	-1.96%	9.99E-01	15 (4.87)	1 (2.63)	-2.24%	9.99E-01
Physical Activity† - *M(SD)*								
Work Activity	2.93 (0.67)	3.18 (0.66)	+0.38	4.19E-02*	2.92 (0.62)	2.82 (0.61)	-0.16	1.37E-01
Free time Activity	2.81 (0.76)	2.47 (0.82)	-0.45	5.70E-03**	2.94 (0.82)	2.39 (0.96)	-0.65	2.30E-03**

Table 3: cont'd

Accidents - *n* (%)								
At work	1 (0.45)	15 (37.5)	+37.05%	6.50E-01	1 (0.37)	1 (3.45)	+3.08%	4.06E-01
In traffic	1 (0.45)	16 (40.00)	+39.55%	1.84E-01	52 (19.33)	1 (3.45)	-15.88%	8.65E-01

Quantitative traits were rank-normal transformed for statistical testing.
ES, Effect size = $(M_{TLS} - M_{MLS}) / SD_{pooled}$
**p*=]0.01; 0.05]=[1.00E-02; 5.00E-02]; ** *p*=]0.001;0.01]=]1.00E-03;1.00E-02]; ****p*=[0.00;0.001]=[0.00;1.00E-03].
†Frequency of physical activity: 1=never; 5=very often.

Table 4: Objective, subclinical health measures in modern living men and women and those living traditionally

Measure	**Men**				**Women**			
	Modern (*n*=251)	**Traditional (*n*=57)**	***ES***	***p***	**Modern (*n*=308)**	**Traditional (*n*=38)**	***ES***	***p***
Blood Measures – Blood Flow - *M(SD)*								
Pulse rate (beats/min)	71.89 (5.62)	74.28 (5.22)	+0.43	1.14E-01	71.95 (5.39)	74.62 (6.29)	+0.49	1.03E-01
BP, systolic (mmHg)	125.58 (17.37)	123.68 (15.66)	-0.11	9.01E-01	120.08 (19.77)	124.74 (20.50)	+0.24	1.30E-01
BP, diastolic (mmHg)	75.31 (7.89)	75.18 (6.88)	-0.02	3.66E-01	72.93 (8.02)	73.95 (6.38)	+0.13	3.78E-01
Blood Measures – Lipid Levels - *M(SD)*								
Total Cholesterol (mg/dl)	220.43 (51.52)	244.40 (45.56)	+0.48	3.10E-03**	225.11 (52.14)	246.29 (44.99)	+0.41	4.89E-02*
LDL Cholesterol (mg/dl)	134.36 (40.31)	152.84 (42.45)	+0.46	1.22E-02*	133.19 (42.64)	146.21 (39.46)	+0.31	1.33E-01
HDL Cholesterol (mg/dl)	54.83 (12.16)	63.04 (16.93)	+0.63	4.20E-03**	66.56 (16.12)	68.76 (14.29)	+0.14	6.18E-01
Triglycerides (mg/dl)	232.28 (179.11)	202.93 (96.82)	-0.18	8.96E-01	166.72 (98.86)	188.16 (106.87)	+0.22	7.22E-02
Lung Function - *M(SD)*								
Peak Expiratory Flow, (l/sec)	8.14 (2.42)	7.89 (2.19)	-0.10	1.36E-01	6.24 (1.73)	5.63 (2.11)	-0.35	2.73E-02*
Forced Expiratory Flow (l/sec)	3.55 (0.95)	3.37 (0.88)	-0.19	4.68E-02*	2.75 (0.74)	2.19 (0.72)	-0.76	3.04E-04***
Forced Vital Capacity (l)	4.37 (1.06)	4.08 (1.05)	-0.28	4.87E-02*	3.25 (0.81)	2.67 (0.80)	-0.72	9.15E-04***
Bone Measures								
Bone Mineral Density (Z-score)	106.16 (24.29)	102.38 (24.18)	-0.16	8.40E-01	100.28 (24.33)	98.09 (28.17)	-0.09	9.26E-01

Quantitative traits were rank-normal transformed for statistical testing.
ES, Effect size = $(M_{TLS} - M_{MLS}) / SD_{pooled}$
**p*=]0.01; 0.05]=[1.00E-02; 5.00E-02]; ** *p*=]0.001;0.01]=]1.00E-03;1.00E-02]; ****p*=[0.00;0.001]=[0.00;1.00E-03].

Table 5: Self-reported health problems in modern living men and women and those living traditionally

Health problem	Men				Women			
	Modern *n* (%)	Traditional *n* (%)	*ES* %	*p*	Modern *n* (%)	Traditional *n* (%)	*ES* %	*p*
Cardiovascular & Metabolic	(*n*=251)	(*n*=57)			(*n*=308)	(*n*=38)		
Hypertension	45 (17.93)	8 (14.04)	-3.90	9.22E-01	68 (22.08)	7 (18.42)	-3.66	6.98E-01
Myocardial Infarction	18 (7.17)	5 (8.77)	+1.60	6.78E-01	15 (4.87)	6 (15.79)	+10.92	2.37E-02*
Stroke	11 (4.38)	3 (5.26)	+0.88	6.28E-01	9 (2.92)	2 (5.26)	+2.34	4.38E-01
Diabetes	16 (6.37)	4 (7.02)	+0.65	8.44E-01	20 (6.49)	4 (10.53)	+4.04	3.56E-01
Kidney Problems	11 (4.38)	0 (0.00)	-4.38	1.53E-01	9 (2.92)	1 (2.63)	-0.29	9.22E-01
Muscoloskeletal Pain	(*n*=222)	(*n*=40)			(*n*=269)	(*n*=29)		
Head	1 (0.45)	8 (20.00)	+19.55	8.59E-01	90 (33.45)	7 (24.14)	-9.32	6.97E-01
Neck	1 (0.45)	10 (25.00)	+24.55	6.94E-01	108 (40.15)	13 (44.83)	+4.68	6.42E-01
Shoulders	60 (27.03)	14 (35.00)	+7.97	2.39E-01	121 (44.98)	11 (37.93)	-7.05	4.68E-01
Elbows	17 (7.66)	5 (12.50)	+4.84	3.09E-01	28.00 (10.41)	3 (10.34)	-0.06	9.52E-02
Wrists	42 (18.92)	10 (25.00)	+6.08	3.69E-01	62 (23.05)	7 (24.14)	+1.09	8.95E-02
Upper Back	1 (0.45)	7 (17.50)	+17.05	9.83E-01	72 (26.77)	3 (10.34)	-16.42	6.37E-01
Lower Back	1 (0.45)	10 (25.00)	+24.55	5.69E-01	86 (31.97)	6 (20.69)	-11.28	1.93E-01
Hip	1 (0.45)	6 (15.00)	+14.55	9.04E-01	52 (19.33)	6 (20.69)	+1.36	6.57E-01
Knees	41 (18.47)	6 (15.00)	-3.47	7.38E-01	59 (21.93)	5 (17.24)	-4.69	7.86E-01
Feet (incl. Ankles)	3 (1.35)	1 (2.50)	+1.15	3.23E-01	1 (0.37)	4 (13.79)	+13.42	4.85E-01

ES, Effect Size = $\text{Percentage}_{TLS} - \text{Percentage}_{MLS}$
*p=]0.01; 0.05]=[1.00E-02; 5.00E-02]; ** p=]0.001;0.01]=]1.00E-03;1.00E-02]; ***p=[0.00;0.001]=[0.00;1.00E-03].

Lung function: All lung function measures (peak expiratory flow, forced expiratory flow, forced vital capacity) showed lower values for TLS compared with MLS participants, with nominally significant differences (all $p<0.05$) for all measures and sexes, except PEF in men, and were highly significant differences in women (Table 4).

Bone mineral density: The *Z*-scaled stiffness index for measuring bone mineral density showed somewhat lower values for TLS men (106.16 vs 102.38) and women (100.28 vs 98.09) but the values were not significantly different (Table 4).

Clinical measures

Cardiovascular and metabolic: Prevalence for various cardiovascular and metabolic diseases (hypertension, stroke, diabetes, kidney problems) showed only minor differences between MLS and TLS participants in men and women. However, a nominally significant increase of myocardial infarction was observed in TLS women (4.87% vs 15.79%, p=0.024, Table 5).

Musculoskeletal: TLS men consistently reported pain more often in various body parts during the week before the examination, with the strongest differences in head (0.45% vs 20.00%), neck (0.45% vs 25%), upper back (0.45% vs 17.50%), lower back (0.45% vs 25.00%), and hip (0.45% vs 15.00%). TLS women, on the contrary, did not report consistently more pain than MLS women. The largest differences existed in TLS women reporting less pain in the head (33.45% vs 24.14%), upper back (26.77% vs 10.34%), and lower back (31.97% vs 20.69%) compared with MLS women. None of the differences proved nominally significant (Table 5).

Discussion

The Northern Swedish Population Health Study (NSPHS) was presented here, a population-representative, cross-sectional study of a rural population in Karesuando, County of Norrbotten, Sweden, in the very north of Sweden north of the Arctic Circle. It is a paradigmatic study in the sense that it attempts to connect two focus areas of research to: (i) provide a survey of the health status and the specific needs of the individuals and the community; and (ii) perform research on novel environmental and genetic determinants of non-communicable diseases on an international level. A summary and discussion follows that present findings on lifestyle differences and health outcomes between modern and traditionally living individuals in the NSPHS study described in this article. Additionally, past contributions of this study to the identification of novel genetic determinants of health relevance in international meta-analysis studies[18-28] are reviewed.

Lifestyle and health – a community-health perspective

Traditionally living men consume much more game meat, less non-game meat and less milk products compared with men of a modern life style. Similar differences in consumption of game and non-game meat are found in women, who also seem to consume fewer vegetables. From a nutritional point of view, the difference in game meat consumption can explain the lower intake of fat and the higher intake of protein in the TLS group. These results corroborate a recent study on lifestyle differences (diet, activity) in a more southward population of the Swedish mountain range[3].

The differences in game and vegetable intake, especially in women, carry two risk factors that can have direct effects on lipid levels and indirectly also affect cardiovascular risk. Although game meat contains much more protein (27.11% vs 17.32%) and less fat (7.36% vs 12.75%) compared with non-game meat, the cholesterol content is specifically higher in game (0.76% vs 0.60%) compared with pork or beef[34]. Furthermore, vegetables are a major source of plant sterols, especially β-sitosterol, which specifically inhibit the uptake of cholesterol in the intestines[44] and are associated with a lower risk for coronary heart disease[45]. Interestingly, it was seen that total, LDL, and HDL cholesterol levels are also consistently increased in individuals with a traditional lifestyle, indicating high risk values for total cholesterol values for approximately two out of three individuals[43]. In agreement with increased cholesterols in TLS, blood pressure tended to be higher in TLS women, and both TLS men and women reported moderately higher pulse rates in contrast to their respective comparison group. A higher prevalence of myocardial infarction in traditionally living women was also seen, an increase that agrees with previous studies[46], whereas no substantial differences in prevalence of cardiovascular or metabolic diseases were found in men.

The observed lower intake of dairy products, especially in men, can negatively affect the bioavailability of micronutrients such as calcium or vitamin D, which are essential for bone health[47]. Heaney et al. even stated that 'it is difficult to devise a diet that is "bone healthy" without including three servings of dairy per day'. Bone mineral density (BMD) of both TLS men and women tended to be lower than in respective MLS comparison groups. The BMD values corresponded well with differences in the intake of dairy products between MLS and TLS men and women, indicating the importance of milk products for bone health.

Traditionally living men seem to be more active at work, but less so during free time than modern living men. Traditionally living women, however, show overall lower physical activity compared with modern living women. Consistently with this higher level of physical activity at work, TLS men also report higher rates of work and traffic accidents than MLS men. An opposite pattern of traffic accidents is found in women, with TLS women reporting fewer problems. The TLS men also reported much higher frequencies of work or traffic related accidents. The fact that opposite effects were observed in the male and female group supports the view that the high frequency in men is due to their high mobility at work. Orthopedic symptoms, in terms of physical pain in various body parts, were increased in men with a more physically demanding lifestyle. However, a similar or lower proportion of pain symptoms were reported in TLS compared with MLS women. The physical location of pain in the body with a high percentage of TLS men reporting pain in the head, neck, back, or hip further strengthens the view that the physical activity of TLS men results in multiple effects. This evidence is supported by qualitative reports on the working life of reindeer herders who describe hard physical labor at cold temperatures and heavy use of snow mobiles. Driving their vehicles at high speed over long distances on bumpy ground to tend their herds causes strong and continuous concussions of the spine. Since their work is highly seasonal this means that there are periods during the year with highly intense work with little time for rest and recreation[2].

Individuals with a traditional lifestyle showed consistently lower lung function than individuals in their comparison group, with larger differences in women. Although these differences require careful interpretation because of the body height differences (highly correlated with lung function) between the subgroups, these results suggest a relationship of less physical activity and increased smoking rates with lower lung function in traditionally living women.

The authors are aware of the limitations of this study regarding the reliability (small sample size, sample size imbalances) and validity (confounders) of the presented results. The application of sophisticated, parametric statistical models to small sample sizes may have caused conservative results. However, considering the complicated data structure the authors are not aware of better statistical models or tools specifically developed within the EUROSPAN consortium to optimally analyze this data[48-50].

In summary, women with a traditional lifestyle have a higher cardiovascular health risk compared with women with a modern industrialized lifestyle, possibly because of the following risk factors: higher age, higher consumption of game meat (low in fat, but rich in cholesterol), lower consumption of vegetables (containing β-sitosterol which inhibits cholesterol uptake), less physical activity (especially at leisure), and higher smoking rates. These differences can explain the elevated prevalence of myocardial infarction in TLS women compared with other females. It is proposed that men with a traditional lifestyle have an overall higher orthopedic health risk compared with men with a modern, industrialized lifestyle, possibly because of increased physical activity at work, and higher frequency of work or traffic accidents. Additionally, the substantially lower consumption of dairy products that is also associated with lower bone health (eg bone mineral density) may contribute to the substantially elevated rates of body pain, especially in the back.

Genetics and health – contributions of local populations to global research

Although environmental influences, such as diet and physical activity, are commonly considered important risk factors for various diseases, genetic variants which can be of similar relevance are less present in public awareness. In the NSPHS study, however, an attempt was made to take into account both environmental and genetic effects on health. Due to the complexity of genetic effects it was only possible to deal with this challenge by collaborating with international consortia where studies are pooled to obtain large sample sizes consisting of tens of thousands of individuals. In particular there was cooperation with the European Special Populations Research Network (EUROSPAN, http://www.eurospan.org) which consists of a number of rural populations from Europe (specifically Sweden, Great Britain, The Netherlands, Italy, and Croatia), but also with other international consortia resulting in several high-impact publications on genetic risk factors.

In cooperation with the partners the present authors have identified genes or gene regions with variants that affect, for example, uric acid clearance[18], lipid levels[19,20] and weight[21]. These results provide in many cases the first insight into the underlying genetic factors of these traits and disorders. Although most of the genetic risk factors known at present are too weak to have an immediate clinical use, they make it possible to identify metabolic pathways of health relevance and point toward novel potential targets for diagnostic tests and therapeutic interventions. Some of the findings that highlight genetic risk factors for metabolic, cardiovascular, and other disease indicators are now summarized.

Results from EUROSPAN/NSPHS

The body mass index (BMI=weight/height^2) is a measure for body fat and an important risk factor for many metabolic and cardiovascular diseases. By joint linkage and genome-wide association analyses, EUROSPAN located a single-nucleotide polymorphism (SNP) close to *MGAT1*, which is associated with weight[21]. A genetic region including the *GHRHR* gene, which affects height[22] was also discovered. These findings were later completed by a second gene, the *JAZF1* gene, also affecting body size[23]. Because this gene also has a key function in the metabolism of growth, *JAZF1* represents one of the strongest candidates influencing human height identified so far. Sphingolipids have essential roles as structural components of cell membranes and in cell signaling. Disruption of their metabolism causes several diseases, with diverse neurological, psychiatric, and metabolic consequences. The results showed that genetic variants in five genomic regions affect sphingolipids and associate with myocardial infarction[19]. Creatinine level in the blood serum is an important indicator of kidney function. A genome-wide linkage analysis of serum creatinine in the EUROSPAN cohorts identified a novel locus in the *MYH9* gene associating with serum creatinine levels[28].

Results from other consortia including EUROSPAN/NSPHS

In a meta-analysis of the CHARGE consortium the role of the *FTO* and *MC4R* genes was confirmed and one novel locus identified in the *NRXN3* gene influencing central abdominal fat[24]. As a member of the ENGAGE consortium the present authors found 22 loci associated with blood serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides[20]. The authors participated in a meta-analysis of 21 studies that identified 16 loci associated with other pre-diabetic traits[25]. A collaboration of 14 studies identified 9 loci, 5 of which were novel, that affect uric acid levels in the blood serum[18]. Finally, in the SPIROMETA consortium the authors discovered a number of gene loci affecting various measures of lung function, for example vital capacity[27].

Future contributions of local populations to the understanding of complex diseases

Because the mainstream of human health research focuses on urban populations, it might be assumed that local, rural, or remote populations with their specific lifestyles and genetic background might be of limited value for basic research. However, there are several reasons why especially these populations can be a great asset in understanding environmental and genetic risk factors for complex diseases, as explained in the introduction. The authors are currently examining the potential of modeling environmental effects in genome-wide association studies on blood lipid levels to strengthen genetic signals and find novel genetic variants. Initial results show that by adjusting for the environmental effect (ie diet, physical activity) additional genetic factors affecting blood lipid levels can be identified[26].

Even if the methodological advantages of studies in rural populations are not harnessed, studies of local populations, such as NSPHS, can still make important contributions to basic research, if they are organized in larger consortia, such as the European Special Populations Research Network (EUROSPAN). These organizations can provide important support to leverage rural studies for participation in large international preclinical and clinical trials. Through this collaboration they may also gain access to resources (eg medical staff, laboratory devices) that will enable population-based health surveys and the identification of specific medical needs of rural or local populations.

Conclusion

In conclusion, there are two points to be highlighted. First, cardiovascular and orthopedic health problems related to sex and lifestyle have been observed in a Northern Swedish population living north of the Arctic Circle. These findings clearly demonstrate the need of rural populations for health assessment and health care. Second, it was found that rural populations feature several advantages for studying the epidemiology of environmental and genetic factors and are suitable participants for large international studies. Studies on environmental and genetic risk factors in rural populations offer great opportunities to better understand the risks for common diseases.

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Appendix I: Supporting documentation[51]

The Northern Swedish Population Health Study (NSPHS) – A paradigmatic study in a rural population combining community health and basic research
(Supporting Text S1)

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Organization. Data collection in a rural population requires taking into account the specific geographical, cultural and historical conditions beyond the usual scientific standards. Therefore, we describe features of the study which were very important in our experience and will presumably also be of interest for other researchers planning similar research.

Ethical approval. The NSPHS study was approved by the local ethics committee at the University of Uppsala (Regionala Etikprövningsnämnden, Uppsala, Dnr 2005:325) in compliance with the Declaration of Helsinki (29). All participants gave their written informed consent to the study including the examination of environmental and genetic causes of disease. In case the participant was not full age, a legal guardian signed additionally. The participants were first informed about the study. Those who signed the informed consent took part in a clinical interview to collect data on sociodemography, lifestyle, subclinical and clinical measures (see Methods) at the same session. A task force on specific ethical problems of isolated populations was created within the EUROSPAN consortium (http://www.eurospan.org > Working Groups). A comparison of the information given in the different informed consent forms used in the EUROSPAN project, in which NSPHS is a partner, with present ethical guidelines has recently been published (30).

Geographic Location and Seasonality. The study site is situated in Karesuando, the northernmost village in Sweden, which is about 1250 km from the coordinating research center in Uppsala and approximately 250 km north of the Arctic Circle. Furthermore, the participants' homes are spread out over a large region with traditionally living persons showing a high degree of mobility. Therefore, the data collection had to be done at a local health center in Karesuando by local staff over a longer period of time to be able to make suitable, individual appointments with all participants.

Especially during the short summer period, male reindeer herders follow their herds wandering around to distant places, which made it necessary to finish data collection before summer. Otherwise, it would have been difficult to adequately represent individuals with a traditional, mobile lifestyle in the sample. Therefore, the data collection took place between January and July 2006.

Culture and Language. In this population mainly three languages are used which are Swedish as the official language, Sami ("nordsamiska"), and Finnish. Although it is common for locals to speak at least two languages, it is not rare to meet persons, especially among the elderly, which are monolingual. Therefore, it was not feasible to hand out self-report questionnaires, but data was gathered during a clinical interview. A trained study nurse who was fluent in all three languages made sure that all questions were fully understood and translated the Swedish-language questionnaires to other languages as necessary.

History. The current Swedish government undertakes great efforts to support and integrate the Sami people with their traditional lifestyle based on reindeer herding into the Swedish society. However, in the past the Sami culture, language, and lifestyle has been treated in a less positive way by Swedish authorities (2). Therefore, feelings of mistrust when dealing with representatives of the "Swedish system" still remain.

We tried to take these circumstances into account by making considerable efforts to explain the purpose and procedures of the study and its benefits for the community and for basic research in a series of information meetings in Karesuando held by the principal investigator. A specific concern was the fact that the project included environmental and genetic analyses and much of the discussion during the initial information meetings focused on the genetic studies. Substantial efforts were made to elucidate to the participants the need to examine both environmental and genetic causes of disease.

During and after the study, results relevant for the individuals were reported to the participants who were referred to a local practitioner if follow-up examination or treatment was indicated. Similarly, group-level results important for community health were presented to the community and discussed with health system officials. Media, such as local newspapers, radio and TV stations, showed a high interest in the project which was covered multiple times[51].

Setting. The local community was informed about the study and asked for their participation in various forms, e.g. during repeated presentations of the study at the community center by the principal investigator (Ulf Gyllensten), during visits at the local health center by the district nurse (Svea Hennix), by reports in local newspapers and radio stations, and by notices on public places. A local team was recruited to enroll participants, and this was headed by the district nurse (Svea Hennix) who had about 30 years of experience of working in this community. The clinical interview and examination took approximately two hours per subject. Data was collected by the district nurse using paper-based questionnaires or directly entered or recorded in electronic format into a database with a graphical user interface based on Microsoft Access 2003.