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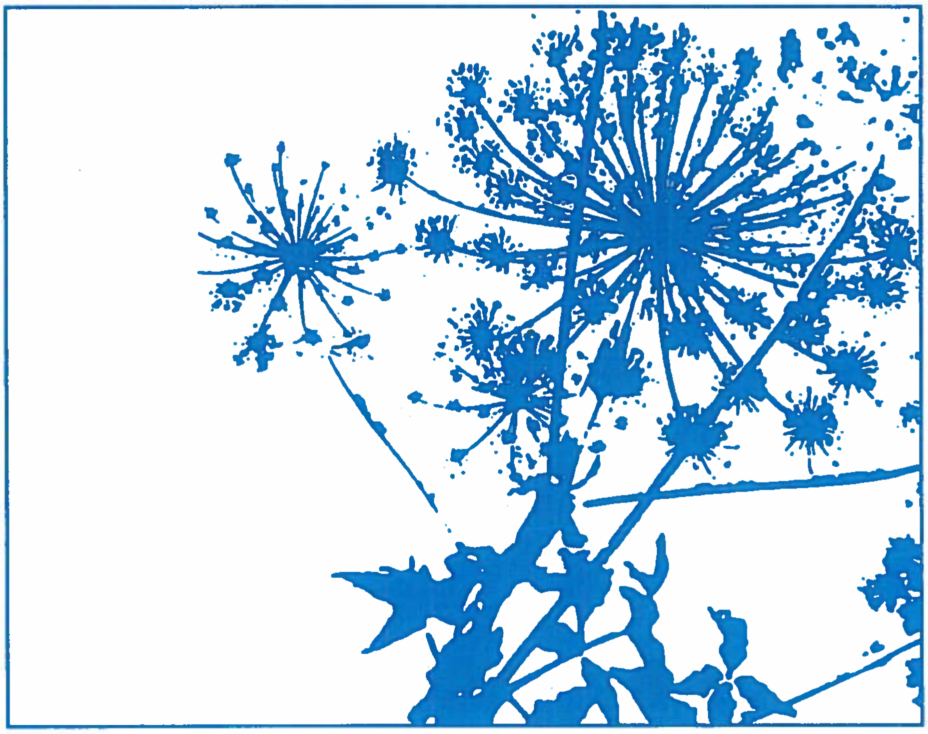

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURE, LIFE-STYLE FACTORS AND PREGNANCY OUTCOME IN ARCTIC AND SUBARCTIC POPULATIONS OF NORWAY AND RUSSIA

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Tromsø 2000

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SUMMARY

Background: The study was initiated because of the public fear of adverse reproductive health and pregnancy outcomes in the Russian-Norwegian border zone in the vicinity of the nickel producing industry in the Kola Peninsula. The original objective was to assess health conditions of delivering women and their outcomes in the general population in the Russian-Norwegian arctic area, including assessment of essential and toxic elements. In the course of the study, the health of an occupationally exposed population of female nickel industry workers and children living in the Kola Peninsula also became an important issue. *Material:* In the period April 1994 - June 1994 maternal information, delivery information, as well as maternal and neonatal blood and urine samples, were collected for approximately 50 deliveries in each of the cities Arkhangelšk, Nikel, and Monchegorsk in Russia; the three Norwegian study centres were Kirkenes, Hammerfest and Bergen. Arkhangelsk was chosen as a large subarctic city without any nickel industry, while Nikel and Monchegorsk were included because of their nickel processing industry. Kirkenes was selected as the closest neighbouring city to the Russian nickel industry, Hammerfest as an arctic coastal city, and Bergen as another sub-arctic city without any metal producing industry, at almost the same latitude as Arkhangelsk. Additionally, in 1995, on request of the local health authorities, medical information and blood samples were collected from children living in Apatity, an industrial city in the Kola Peninsula, and in the two remote indigenous villages Lowozero and Kraschnochelie. *Results:* Urinary nickel concentrations were significantly higher in the Russian study groups. Sources of nickel exposure for the Russian population which explain this remain unidentified. Environmental nickel exposure, as measured by urinary nickel excretion, was not shown to be a predictor variable of low birth weight nor of the newborn child's body mass index (BMIC). The mineral status of delivering women in arctic and sub-arctic areas of Norway and western Russia was adequate, with the exception of zinc. The variation of serum zinc concentrations demonstrated differences between arctic and sub-arctic areas across national borders. Maternal serum zinc was a positive predictor variable for birthweight. Maternal blood lead was a negative predictor of birth weight, even at the rather low concentrations in this study. The inclusion of maternal lead in a multivariate model caused the non-specific country difference to loose statistical significance. Blood lead concentrations in schoolchildren living in remote areas of the Kola Peninsula were up to a level of medical concern. The mean birth weight and BMIC were significantly lower in the Russian study groups, suggesting the likely occurrence of nutritional deficiencies during pregnancy in Russia. Congenital malformations were too scarce to be assessed. However, this observation does not address the concern about reproductive and developmental health effects, neither in the general population nor in the higher exposed women working in the Russian nickel industry. Monchegorsk nickel refinery workers are heavily exposed to nickel, and maternal employment in a nickel refinery must be explored further as a risk factor for adverse reproductive outcomes. Well-designed, comprehensive epidemiologic studies of reproductive and developmental health among Russian nickel refinery workers are warranted, technically feasible and ongoing. *Conclusions:* No effects of the studied pollution factors, except for the negative impact of maternal lead concentrations, could be observed on the pregnancy outcomes, birth weight and BMIC. The statistically significant difference between the Norwegian and Russian mean BMICs suggests that malnutrition during pregnancy might occur in the Russian study groups. Blood lead concentrations up to a level of medical concern were observed in children living in remote areas of the Kola Peninsula.

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PREFACE

This work started with a man knocking on my door at the Kirkenes hospital just before Christmas in 1990. It was Alexander Duriagin, Head Doctor of the Nikel hospital, who gave me a bread as a symbol of friendship. At that time the public attention was drawn to possible health effects of the industrial pollution at the Kola Peninsula, especially concerning pregnancy complications and congenital malformations. The idea developed further from Marie Hallonen's input every morning at the delivery department meeting, leading to contact with former collegue Knut Dalaker. A preliminary study protocol was formulated and the first blood and placentas were collected in Kirkenes and Nikel. Private reasons made us leave Kirkenes, and I thought the whole initiative might have to be left as a good idea and nothing more. The samples were stored in Kirkenes, Hammerfest, Tromsø, and, finally, Bodø. Shortly after our move, Eiliv Lund was contacted by the Secretariate of the Arctic Monitoring and Assessment Programme (AMAP) with a request for help in the Subprogramme on Human Health. In a meeting with Tor Norseth at the National Institute of Occupational Health (NIOH) I was introduced to Yngvar Thomassen, who later introduced me to Evert Nieboer, bringing three important contributors into the project. At the same time, Valery Petrovitch Tchachtchine was involved in the planning of the Norwegian-Russian Health Study, and started to open doors in Russia. Due to a grant from the Royal Norwegian Foreign Department, East-European Secretariate, we were able to invite Natalya Romanova from St.Petersburg to be trained and conduct the elemental analyses at NIOH. Anatoly Tkachev was already connected to the Institute of Community Medicine, University of Tromsø, providing important contacts in Arkhangelsk County. The late Jens Peder Hart Hansen introduced me to Jens C. Hansen and Peter Bjerregaard in the Danish AMAP-Human Health Group. The ideas turned out to be very close to this author's ideas, and the protocols were revised to fit into the same program. With the established cooperation between the Danish collegues and the Canadian collegues Andy Gilman and Eric Dewailly we suddenly had covered most of the arctic circle. Valery Klopov provided us with his contacts in remote areas of Siberia. Irina Perminova facilitated access to the small indigenous villages at the Kola Peninsula together with Svetlana Belova. Per-Einar Fiskebeck was employed as a »field man» of the Norwegian-Russian Health Group, and generously provided much of his time and his Volkswagen van for our work.

During the period November 1993 – June 1997, I was a Research Fellow at the Institute of Community Medicine, University of Tromsø, interrupted by 6 months as a lecturer in epidemiology at the Institute. I probably learned more epidemiology than the students.

AKNOWLEDGMENTS

I wish to express sincere appreciation to the following people (if someone has been coincidentally forgotten, please forgive me): First of all, my supervisor Eiliv Lund, the co-supervisor Tor Norseth, and in the last phase the substantial contribution from Evert Nieboer; in Kirkenes hospital Marie Hallonen and all friends and collegues at the delivery department, Jan Eirik Løkebø and Harald Sunde for good assistance in the initial phase of the project; in Hammerfest hospital Emil Nussler, Jan Brox, Kåre Augensen, the midvifes at the delivery department, and the good helpers in the clinical-chemical department; Per-Einar Fiskebeck at the County Governor Office of Finnmark for logistical assistance and many good jokes; at the University of Tromsø, Eiliv Lund, Tone Smith-Sivertsen, Bjørg Hunstad, Anna-Kirsti Jensen, and, especially, Henrik Schirmer for sharing my office and answering telephone calls from Russia; at Nordland Central Hospital the staff of the Womens Clinic for giving me opportunity to finish this work after returning to clinical practice, and the collegues at the Department of Immunhematology and Transfusion Medicine for taking care of my freezer; at Haukeland hospital Knut Dalaker and the staff at the delivering department; and the excellent staff at NIOH, especially Yngvar Thomassen, Gunhild Sand, and Natalya Romanova; at the Nikel hospital, Alexander Duriagin (thank you for the bread and many important toasts!), Elvira Khotova, Leonid Zhivakov, Irina Zhivakova, and the staff at the delivery department; in Murmansk Regional Hospital and later at the Murmansk Regional Administration Igor Kovalev; at the Kola Research Laboratory of Occupational Health Valery P. Tchachtchine and all his staff, including the excellent drivers; at the Kola Science Center Gennadi Kalabin and Irina Perminova; in Arkhangelsk Anatoly Tkachev and Jevgenij Bojko; and in St.Petersburg, Valery Klopov.

Liv-Helen, Svein Øyvind and Maria Lisa eventually became accustomed to a husband and father with too many crazy ideas, and in his absences have also developed a certain experience in handling strange telephone calls from Siberia.

This work has been supported by The Royal Norwegian Foreign Department, East-European Secretariate; The University of Tromsø, Steering Group of Medical Research in Finnmark and Nordland; the Aakre's Foundation, University of Tromsø; and the Barents Secretariate. This report is finally dedicated to all the delivering women in Norway and Russia, who were willing to contribute to this study based on everlasting concern, love and care for their children.

LIST OF PAPERS

I. Odland JO, Nieboer E, Romanova N, Thomassen Y, Norseth T, Lund E. Urinary nickel concentrations and selected pregnancy outcomes in delivering women and their newborns among arctic populations of Norway and Russia. J Environ Monit 1999; 1: 153-161.

II. Odland JO, Nieboer E, Romanova N, Thomassen Y, Brox J, Lund E. Essential elements, birth weight and newborn body mass index in arctic populations of Norway and Russia. Acta Obstet Gynecol Scand 1999; 78: 605-614.

III. Odland JO, Nieboer E, Romanova N, Thomassen Y, Lund E. Blood lead and cadmium and birth weight among sub-Arctic and Arctic populations of Norway and Russia. Acta Obstet Gynecol Scand. In press.

IV. Odland JO, Nieboer E, Romanova N, Thomassen Y, Brox J, Lund E. Selfreported ethnic status of delivering women, newborn body mass index, and blood, serum and urine con centrations of toxic and essential elements in Norwegian and Russian arctic populations. Int J Circumpolar Health 1999; 58: 4-13.

V. Odland JO, Perminova I, Romanova N, Thomassen Y, Tsuji LJS, Brox J, Nieboer. Elevated blood lead concentrations in children living in isolated communities of the Kola Peninsula, Russia. Ecosystem Health 1999; 5: 75-81.

VI. Odland JO, Tchachtchine VP, Bykov V, Fiskebeck PE, Lund E, Thomassen Y, Nieboer E. Critical Evaluation of Medical, Statistical and Occupational Data Sources in the Kola Peninsula of Russia Pertinent to Reproductive Health Studies. Arch Environ Occup Health 1999; 72: 151-60.

ABBREVIATIONS

ANOVA – Analysis of variance

AMAP – Arctic Monitoring and Assessment Programme

BMI – Maternal body mass index - kg/m^2

BMIC – Childrens body mass index - kg/m^2

CBCd – Cord Blood Cadmium

CBPb – Cord Blood Lead

DL – Detection Limit

HELLP – Hemolysis Elevated Liver enzymes Low Platelet count

MBCd – Maternal Blood Cadmium

MBPb – Maternal Blood Lead

NIOH - National Institute of Occupational Health

PROM – Premature Rupture of Membranes

QA – Quality Assessment

QC – Quality Control

SIDS – Sudden Infant Death Syndrome

ERRATA

Paper I, Table 6, column 2: «Change in birth weight/g», corrected to «Change in child's body mass index (BMIC) kg m^{-2}».

Paper II, p. 607, column 1, line 6-7: «, and specimen collection» should be deleted.

Paper II, p. 610, column 1, line 5 from the bottom of page: replace p=0.002 with p=0.03.

Paper III, p. 860: Reference 54 is wrong. The correct is:

Nieboer E, Tchachtchine VP, Odland JO, Thomassen Y. Reproductive and Developmental Health in Relation to Occupational Exposure to Nickel in the Kola Peninsula of Russia: A Feasibility Study. Hamilton, Canada: McMaster University, 1997 (unpublished).

Paper IV, p. 10, reference 6: «Environ Monit» change to «J Environ Monit».

Paper IV, p. 12, line 25: «<21 nmol/L» change to «<12 nmol/L».

Paper IV, p. 12, line 26: «for 2 fish meals» change to «≥2 fish meals».

INTRODUCTION

The Concern of Newborn Children in the Norwegian-Russian Border Area

A real public concern about pregnancy outcome has developed during the last decade in relation to the substantial emissions of sulfur dioxide and metals by the nickel industry in the Kola Peninsula. Nearly half of the aerosol emission is nickel, with iron and copper as other major contributors (Sivertsen et al. 1992; Hagen and Sivertsen 1992; Norseth 1994; Smith-Sivertsen et al. 1997). Extensive environmental damage has resulted from these pollutants. Furthermore, a preliminary study (Chashschin et al. 1994) indicated increased spontaneous abortions, premature deliveries, low birth weight or congenital malformations in the children of occupationally exposed female nickel workers.

The Norwegian-Russian Health Initiative

A Norwegian-Russian Commission on Environmental Cooperation was established in 1988, which encouraged extensive investigation of the pollution of air, water, soil and biota. By contrast, very little was planned for the study of human health. In 1989, health officials of the Kola Peninsula and Finnmark County met in Kirkenes to discuss possible environmental and health impacts of the pollution associated with the nickel production in the Kola Peninsula. Subsequently, collaboration was initiated that primarily addressed environmental impacts. As a result of the increasing worry about human health in the area, it was included as an issue of investigation in the bilateral monitoring programme in 1992. The health group under the Joint Norwegian-Russian Environmental Commission decided to carry out a cross-sectional health study among adults in Sør-Varanger, Nikel and Zapolyarniy in order to investigate the possible negative health effects of the nickel and sulphur dioxide emission. The results of this study were published by Smith-Sivertsen et al. (1997). It focused on asthma and chronic obstructive lung disease, nickel allergy, other allergic diseases, but to a minor extent adverse outcomes of pregnancy. Parallell to this bilateral effort, the Arctic Monitoring and Assessment Programme (AMAP) was initiated, which emphasized environmental contamination but included pregnancy outcome assessments as a minor component (Odland et al. 1996; Odland et al. 1997; AMAP 1998). These latter three publications present original data on the levels of toxic and essential elements in human material and, very briefly, pregnancy outcomes from the Norwegian-Russian arctic areas.

The Purpose of the Study

This study was planned to assess health conditions of delivering women and pregnancy outcome in the general population of the Russian-Norwegian border area, including assessment of toxic and essential elements in women and their newborn children. During the project, adverse pregnancy outcomes in exposed workers of the nickel industry became evident and the need for a more comprehensive epidemiological study of it was indicated. The first component could be initiated immediately by establishing a network of colleagues at the different delivery departments in the study. The other needed a feasibility study requiring the close cooperation with medical and supervisory personnel in the nickel industry.

GENERAL BACKGROUND

In the remaining sections of the Introduction, topics pertaining to the thesis are briefly introduced. For most of the areas reviewed, only key references are provided. More extensive coverage is provided in the published papers that form the basis of this thesis.

Birth Weight and BMIC as Pregnancy Outcomes

Birth weight is recognized as an important indicator of the health status of neonates. Temporal changes in this parameter may serve as an index to socio-economic conditions that impact on reproductive and developmental health (Bantje 1986; Cole et al. 1997; Cole et al. 1998). On the other hand, the newborn child's body mass index (BMIC=kg/m^2) has been suggested to have some advantages as an index of the nutritional status of newborn children (Wandja et al. 1995). BMIC constitutes a measure of body fatness (Gallagher et al. 1996). Both parameters have proved their usefulness in studies with relatively small sample size, reliability across national, social and cultural borders; there is also substantial evidence for their importance in the implementation of pregnancy care and assessment of pregnancy outcome (Antonisamy et al. 1994; Balla and Walia 1996; Chard et al. 1997; Cole et al. 1998). Other parameters, like spontaneous abortions and congenital malformations are more sensitive to the thoroughness of reporting (Medical Birth Registry of Norway 1997), and a substantially larger sample size is needed to evaluate enhanced prevalence or incidence (Nieboer et al. 1997). Since BMIC effectively corresponds to birth weight adjusted for length or height (Forsdahl 1986), it is relevant to review the known determinants of birth weight.

Determinants of Birth Weight

Gestational age

Gestational age is an outcome factor that strongly influences birth weight (Ramakrishnan et al 1999). In a Tanzanian study (Bantje 1986), it was suggested that short gestation accounted for 70 % of all cases with low birth weight. For intervention purposes prophylactic measures to reduce preterm deliveries are of the highest importance, as discussed by Holt et al. (1999) for northern Norway.

Genetic and anthropometric aspects

Mongelli (1996) has discussed maternal lean body mass index and birth weight, adjusted for maternal weight and height, smoking, parity, gestational age and sex of the infant. It was shown that only cigarette smoking had a negative effect on birth weight which was independent of maternal anthropometry. It was concluded that the effect of maternal size on birth weight is largely mediated through constitutional and genetic factors rather than nutrition. Maternal birth weight has been shown to be an important predictor of infant weight at birth (Tavares et al. 1996; Ramakrishnan et al. 1999).

Maternal height has been demonstrated to effect both birth weight and birth length from week 35 onward (Witter and Luke 1991). The infants of the shorter women were symmetrically smaller than the infants of the taller women as the infant Ponderal Indices (weight /$(\text{length})^3$) did not differ.

Wilcox et al (1996), in a comparison of perinatal mortality data in the United States and Norway, have demonstrated that a woman is more likely to deliver a heavier baby in her second pregnancy than in her first pregnancy. However, maternal physiological factors differ in the two pregnancies and these differences have additional effects on birthweight. Clinical decisions cannot be based on the assumption that a second baby will inevitably be heavier than the first baby.

Brooks et al. (1995) have investigated the relative role of environmental and genetic factors in the determination of birth weight following ovum donation, showing that the only discernible factors significantly influencing birth weight were gestational age and the recipient's (maternal) weight. Donor's weight, own birth weight or the birth weight of the donor's children were not significantly correlated with the birth weight of the child following ovum donation. The environment provided by the human mother seems more important than her genetic contribution to birth weight.

Paternal influence on birth weight has been demonstrated. In a historical cohort study of girls born in Copenhagen during 1959-1961 (Klebanoff et al. 1998) it was demonstrated that, independently of maternal size, the father's physical stature, particularly his own size at birth, influenzes the birth weight of his children. Furthermore, in a study of paternal influences on birth weight in Nottingham, England (Wilcox et al. 1995), it was demonstrated that after adjustments only paternal height remained significant in a multiple regression. The conclusion was that this effect of paternal height on birth weight must be genetic and therefore should be taken into account when defining intra-uterine growth retardation and macrosomia.

The Renfrew and Paisly Study in Scotland (Davey Smith et al. 1997) concluded that birth weight of offspring was inversely related to mortality. The strength of this association was greater than would have been expected by the degree of concordance of birth weights across generations, but an extensive range of potential confounding factors could not account for the association. Mortality is influenced by a factor related to birth weight that is transmissible across generations.

There is no reliable information regarding genetic differences in Norwegian and Russian birth weights. An interesting aspect is the documented stronger increase in mean height of the Sami population of Finnmark compared to Norwegians, possibly due to developing social-economic conditions in the society (Forsdahl et al. 1994).

Miscellaneous factors

The impact on birth weight of maternal health, environmental and occupational exposures, and sociodemographic factors are discussed in the sections that follow in the wider context of determinants of other pregnancy outcomes.

Maternal Health and Pregnancy Outcome

Maternal weight gain

In the WHO collaborative study of maternal anthropometry and pregnancy outcome (Kelly et al. 1996), poor maternal weight gain in the second trimester was demonstrated as the most practical screening instrument for the risk of low birth weight and intrauterine growth retardation. The operational value of this finding is its practicability, even in difficult social conditions. Wolfe et al. (1991) in Detroit and Karim and Mascie-Taylor (1997) in Dhaka, Bangladesh reach the conclusion that the calculation of maternal body mass index (BMI) offers no advantage in estimating pregnancy outcome over simply weighing the mother. In general, the use of BMI is inadequate without supplementing with height or weight adjustments in epidemiological assessments (Michels et al. 1998). BMI, generally speaking, is demonstrated to be age and sex dependent, but independent of ethnicity (Gallagher et al. 1996).

Hypertensive disorders in pregnancy

Hypertensive disorders during pregnancy comprise several conditions, varying in severity and prognosis (Erkkola 1997). They include: 1) secondary or essential hypertension commenced prior to pregnancy; 2) rise in blood pressure during pregnancy even before the 20th week; 3) elevated blood pressure with proteinuria which may or may not be a consequence of some underlying disease; 4) transient increase in blood pressure after birth; and 5) eclampsia. The resulting HELLP-syndrome is a serious condition of pregnancy; an acronym for hemolysis, elevated liver enzymes, and low platelet count. It might, however, be brought about also by other conditions, as the underlying pathologic processes are primarily hepatic, renal, or coagulation disturbances.

Sociodemographic and Occupational Aspects of Pregnancy Outcome

A first comprehensive Norwegian study of occupational status and pregnancy outcome was published by Bjerkedal (1980), comprising all births reported to the Medical Birth Registry in 1970-1973. The analysis revealed that rates of perinatal death, birth weight less than 2500 g, gestational age less than 37 weeks and congenital malformations were higher among births of economically active mothers than among births of those economically inactive. Generally speaking, birth of mothers engaged in industrial work had the highest risk of perinatal death, low birthweight (<2500 g) and preterm delivery.

Arntzen et al. (1996a) have studied the trends in Norway of associations between maternal education and postneonatal mortality for the period 1968-1991. The inverse association between educational level and postneonatal mortality has strengthened over time, but the underlying causes are hard to determine and are indicative of the complexity of using maternal educational level as an indicator of social status. The same authors have also discussed marital status as a risk factor for fetal and infant mortality (Arntzen et al. 1996b). They have shown that marital status is still a demographic risk factor in the Norwegian welfare society. There is a need to identify specific risk behaviours associated with the life styles of unmarried mothers. Postneonatal mortality in lower social groups can be explained by an association with SIDS (Arntzen et al. 1995).

Wergeland and Strand have discussed the need for job adjustment monitoring in pregnancy outcomes (Wergeland and Strand 1998). Using the risk of preterm birth as the outcome, maternal work history can allow early prediction of need for job adjustment during pregnancy. The same authors have also discussed strenous working conditions and birth weight (Wergeland et al. 1998). It was concluded that strenous work increased the risk of low birth weight in nulliparae, particularly in non-smokers. An inability to alter work pace was the strongest risk factor. The preventive effect of job modification during pregnancy may even parallell smoking cessation.

Hansteen et al. (1998) have demonstrated a significantly lower arithmetic mean birth weight for newborns in a Norwegian industrial area compared to urban and rural non-industrial areas, after controlling for gestational age, sex, parity, maternal smoking frequency and social class. Of the factors considered, only maternal psychological stress at work had a significant effect on birth weight. It was further concluded that birth weight may represent a potential outcome parameter for surveillance of effects on humans of environmental exposures.

Effects on birth weights of maternal education, socio-economic status, and employment conditions are also thoroughly considered in a prospective, population-based study in Uppsala County, Sweden (Nordstrøm and Cnattingius 1996). These authors found that practically all social differences in birth weight are related to the differences in maternal age, parity, height, and smoking habits. The only socio-economic indicator that could be included, mostly for international comparisons, was education.

The ALSPAC Study Group (Farrow et al. 1998) have examined birth weight of term infants and maternal occupation in a prospective cohort of pregnant women. Despite the abscence of a significant association between birth weight and job after adjustments, there were several findings which support the earlier proposed connections between maternal occupation and pregnancy outcome. The major job groups with lower birth weights were metal forming or welding, electric or electronic work, textile trade, and assembling and working with equipment.

A study of perinatal outcome according to residence area in the city of Malmø, Sweden (Gudmundson et al. 1997) concluded that although maternity care is provided free of charge, perinatal complications, including low birth weight, were more frequent in areas of lower socioeconomic status. In order to improve perinatal outcome, antenatal surveillance should be intensified in lower class socioeconomic groups. Vagero et al. (1999) have recently shown that processes during the foetal period are systematically linked to the social circumstances of the mother, being very different when comparing the 1920s to the 1980s.

MacLeod and Kiely (1988) have demonstrated that birth weight increases from parity 1 to parity 3, but drops markedly thereafter. Adjusting for gestational age, age and parity were found to influence birth weight by affecting fetal growth rather than the length of pregnancy.

In studies of American populations, social and class factors are shown to be more predictive of low birth weigth than medical factors alone for women without chronic health problems (Longo 1999). It is interesting that in the Pune district of India, Hirve et al. (1994) have shown in a community-based cohort study that selectively targeted interventions such as improving maternal education and nutrition, wider availability of contraception to delay the first pregnancy and increasing pregnancy intervals may help in identifying and ensuring adequate care for women with the greatest risks of producing low-birth-weight-babies.

Environment and Pregnancy Outcome

Nickel

A range of effects of nickel compounds have been reported in animal experiments (Sunderman et al.1983; Environmental Protection Agency 1985; Sager et al. 1986; Coogan et al.1989). Nickel salts are toxic to spermatozoa and embryos. Nickel is known to cross the placenta in rodents, with reported malformations at birth including ocular, skeletal, and neuronal effects; fetal hemorrhages and hematomas are also reported. Experiments with nickel tetracarbonyl provide the clearest indication of teratogenicity manifesting as ocular effects (anophtalmia and microphtalmia; Sunderman et al. 1979; Sunderman et al. 1980; Nieboer et al. 1988). Chloride salts of Ni^{2+}, have been shown to be embryotoxic and teratogenic in the FETAX assay (frog embryo teratogenesis assay: Xenopus); observed effects included ocular malformation (Hauptman et al. 1993; Luo et al. 1993). Effects on human reproduction have not been demonstrated so far, but the concern has been raised by Chashschin et al. (1994) for occupationally exposed female nickel workers in the Kola Peninsula.

Cadmium and maternal smoking

Animal data suggest that oral exposure to cadmium results in reduced birthweight and more severe effects on the fetus, including placental damage (WHO 1992), embryotoxic and teratogenic effects (Hauptmann et al. 1993; Luo et al. 1993). Evidence in humans of suppression of birth weight by cadmium is difficult to separate from the impact of smoking. It seems that the human placenta serves as a selective barrier to cadmium with an average attenuation of 40-50 % (Lauwerys et al.1978; Roels et al. 1978; Baranowska 1995). Individual variability related to metallothionein induction in the placenta might be operative.

Animal data support this conclusion, with free transport of cadmium through the Wistar rat placenta, while the hamster placenta is totally blocked (Tsuchiya et al. 1987; Hanlon and Ferm 1989).

Maternal smoking might be regarded both as a maternal life-style factor and a fetal environmental factor. There is a wealth of information showing the negative impact of maternal smoking on birth weight. Shu et al. (1995) conclude that maternal smoking at any point in the pregnancy, but especially in the early months, causes low birth weight. Bjerregaard and Hansen (1996) discussed effects of smoking and marine diet on birthweight in Greenland. Smoking was found significantly correlated with low birthweight, while consumption of marine mammals, maternal or cord blood mercury concentration were not. Studies of smoking habits among pregnant women in Trøndelag, Norway, have been performed by Eriksson et al. for the periods 1987-1994 and 1994-1995 (Eriksson et al. 1996; Eriksson et al. 1998). There has been a significant reduction in smoking prevalence among pregnant women in the study area that could not be observed among non-pregnant women. Significant impact of national campaigns against smoking during pregnancy could not, however, be discerned. A low cigarette consumption prior to the pregnancy was the best predictor for smoking cessation during pregnany.

Lead

The major environmental source of lead has been the use of lead in gasoline. In the USA there has been a substantial decline in blood lead levels in the last two decades, because of the removal of lead from gasoline and soldered cans (Brody et al. 1994; Pirkle et al. 1994; Pirkle et al. 1998). This reduction has also been demonstrated in Norway and Sweden (Clench-Aas et al. 1990; Stromberg et al. 1995; AMAP 1998). The main environmental health concern about lead is the impact on perinatal neurodevelopment, expressed subsequently as cognitive and behavioural deficits in the developing child (Silbergeld 1991; Rice and Silbergeld 1996; Recknor et al. 1997). Such central nervous system effects are also seen in children that are exposed to lead in childhood. The placenta barrier exhibits free transfer of lead from the twelfth week of gestation and continues throughout pregnancy (Schramel et al.1987), and it is also apparent that pregnancy increases the mobilization of lead from maternal skeleton, thereby increasing fetal exposure (Silbergeld 1991; Lagerkvist et al. 1993; Lagerkvist et al. 1996; Gulson et al. 1997; Gonzales-Cossio et al. 1997). The accepted level of medical concern for children of 0.48 µmol/L is contradictory to recent studies which show that blood lead concentrations below this value may impair hearing and nerve conduction in the auditory system (Schwartz and Otto 1991). The occurrence of subclinical effects suggests that there may be no safe level of lead exposure for children (Todd et al. 1996). A number of other effects on human health are recognized, including inhibition of blood formation, reproductive deficits, slowing of nerve conduction and renal toxicity (Mushak et al. 1989). Epidemiologic studies suggest that chronic low-level lead exposure may be linked to evelated blood pressure (Schwartz 1991).

Diet and Pregnancy Outcome

Carbohydrates and proteins

Health in later life may already partly be determined by children's intrauterine growth and development patterns (Hautvast 1997). The theory that nutritional and environmental factors during pregnancy are predisposing for certain diseases in adult life is discussed in several publications by the Barker Group (Godfrey and Barker 1995; Godfrey et al. 1996; Godfrey et al.1997; Barker 1997; Barker and Clark 1997; Barker 1998). Godfrey et al. (1996) conclude that high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with with a low dairy protein intake in late pregnancy. Such an effect could have long term consequences for the offspring`s risk of cardiovascular disease or diabetes. There are critical windows of time during which maturation must be achieved, and failure of maturation is considered largely irrecoverable (Barker 1998). These conclusions are controversial, but they clearly represent a renaissance of maternal nutrition research (Brown and Kahn 1997). However, the role of socio-economic factors during childhood and adulthood is not discussed in the »Barker hypothesis» (Rey and Bresson 1997). Forsdahl has discussed living conditions in childhood and subsequent development of risk factors for arteriosclerotic disease (Forsdahl 1977; Forsdahl 1978; Forsdahl 1986). His findings indicate that poverty in childhood and adolescence, followed by later prosperity, results in high cholesterol values. A significant positive correlation between infant mortality rates and later mortality rates from arteriosclerotic heart disease has been demonstrated in Forsdahl`s studies.

Essential elements

The concentrations of most essential elements and nutrients (including vitamins) in body fluids change during pregnancy (van Buul et al. 1995). Interpretation of laboratory tests should be made with caution. However, population-based reference intervals for trace elements in blood are nevertheless useful to explore geographic and temporal variations (Grandjean et al. 1992). In a general overview, Luke (1994) discusses specific nutrients associated with growth retardation, such as vitamin A, folate, and iron. Elevated serum ferritin might even be associated with early spontaneous preterm delivery (Tamura et al. 1996). By contrast, supplementation with calcium and magnesium may increase birthweight and gestational age (Luke 1994). A positive effect on birthweight of food supplementation of essential nutrients in pregnancy has been demonstrated by Metcoff et al. (1985), especially protecting fetal growth in smokers. A recent study by Scholl et al. (1997) of prenatal multivitamin/mineral supplements during the first and second trimesters of pregnancy appears to be connected with a reduction in preterm deliveries and risk of low birth weight in low income, urban women.

Martin-Lagos et al. (1998) have demonstrated a progressive decrease in serum zinc with gestation. Neggers et al. (1990) suggest, based on a study of maternal zinc concentrations and birthweight in Alabama, USA, that there is a treshold for maternal serum zinc below which the prevalence of low birth weight increases significantly. They concluded that maternal serum zinc concentration measured early in pregnancy could be used to identify those women at higher risk of giving birth to a low-birth weight infant. The same authors (Neggers et al. 1991) calculated, based on a retrospective follow-up study, that for each µmol/L increase in serum zinc early and later in pregnancy, birth weight increased by 38 and 56 g, respectively. The larger the reduction in serum zinc during pregnancy, the smaller the infant. This study also suggested a treshold for maternal zinc below which the prevalence of low birth weight increases rapidly. Goldenberg et al. (1995) conclude that daily zinc supplementation in women with relatively low plasma zinc concentrations in early pregnancy is associated with higher birth weights and head circumferences, but the effect occurs predominantly in women with a body mass index <26 kg/m^2. Adding to these conclusions, Friel et al. (1993) have proposed that zinc-supplementation in early infancy may be beneficial for very-low-birth weight infants.

The mentioned study by Martin-Lagos et al. (1998) has also demonstrated a significant increase in serum copper concentrations during human pregnancy, especially in the second and third trimester, independent of the subject`s age. Infections or inflammatory conditions might further increase the plasma or serum concentrations (Burtis and Ashwood 1994). Animal studies (Vaquero and Navarro 1996) confirm that moderate food restriction during pregnany produces intrauterine growth retardation and that newborns have low trace element contents, especially copper. This is probably connected to the role of copper as an essential constituent of many enzymes and important proteins (daSilva and Williams 1991). Dietary sources might be parenchymatous tissues, like liver, seefoods, nuts and seeds (USA National Research Council 1989).

Selenium is a component of a number of crucial enzymes, and deficiency has been linked to ill health, like cardiovascular diseases, osteoarthritis and cancer (Burtis and Ashwood 1996). In a recent study, Navarro et al. (1996) document a moderate decrease in serum selenium concentrations during pregnancy. No significant differences could, however, be shown between the pregnant and non-pregnant group, nor between the groups in different trimesters of pregnancy. No selenium problems in daily dietary intake with respect to maternal and fetal needs during pregnancy were documented by these authors.

Alcohol abuse

Alcohol use or abuse is still a controversial subject. Sampson et al. (1994) concluded that neither birth weight nor any later size measure was as useful an indicator of the enduring effects of prenatal alcohol exposure as were certain neurodevelopmental outcomes. Shu et al. (1995) conclude that moderate alcohol drinking possibly is a cause of low birth weight. Stoler et al. (1998) have studied two new markers of alcohol use, whole blood-associated acetaldehyde and carbohydrate-deficient transferrin, and two traditional markers namely gamma-glutamyl transpeptidase and mean red blood cell volume in the blood of pregnant women. The infants of mothers with two or more positive markers had significantly smaller birth weights, lengths, and head circumferences than the infants with negative maternal screens. The presence of two or more positive markers was more predictive of infant outcome than any self-reported alcohol use.

MATERIALS AND METHODS

Details of the study populations, procedures, sample collection and analyses are given in the individual papers. The geographical areas are shown in Figure 1. Table 1 summarizes the geographical areas, number of subjects, types of samples collected and analyzed, and the main focus for Publications I to VI. Information was also collected from personal questionnaires completed in an interview (see Appendix I) and medical records.

The study was approved by the Regional Ethical Committee, University of Tromsø, Norway, the Norwegian Data Inspectorate and the Regional Health Administrations of Murmansk and Arkhangelsk Counties. The women were asked to join the study by completing a consent form (see Appendix II).

Fig. 1. Map of the Barents Region, showing important locations described in the study.

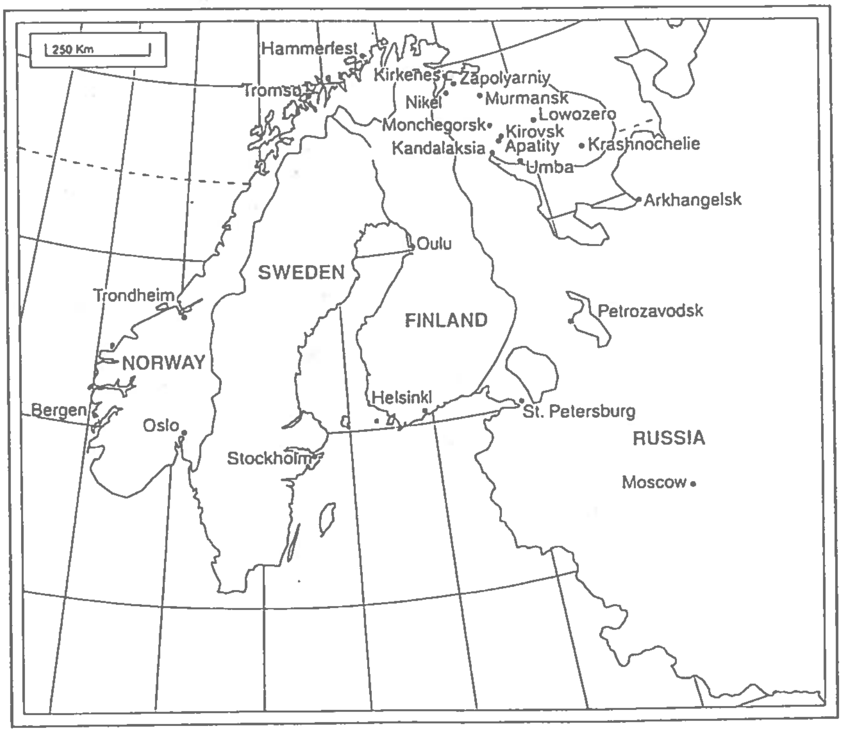

Table 1. Geographical areas, subjects, type of samples collected and analyzed, and the main focus for Publications I to VI.

Site (period)	Subjects (N), Paper	Samples	Analytes	Main focus
Kirkenes (November 1993 – January 1994)	46, I 51, II 19, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Hammerfest (December 1993 – January 1994)	51, I 56, II 48, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Bergen (June 1994)	31, I 60, II 47, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Finnmark/Kola Peninsula (November 1993 – June 1994)	15, IV	Urine Serum Blood	Nickel, creatinine, copper, ferritin, selenium, zinc, cadmium, lead	Ethnic differences in essential and toxic elements and pregnancy oucome
Nikel (March - June 1994)	42, I 50, II 49, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Monchegorsk (March – June 1994)	49, I 50, II 49, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Arkhangelsk (April – May 1993)	46, I 51, II 50, III	Urine Serum Blood	Nickel, creatinine Copper, ferritin, selenium, zinc Cadmium, lead	Essential and toxic elements and pregnancy outcome
Apatity (March 1995 and November 1995)	39 (group 1), V 24 (group 2), V	Serum Blood	Ferritin Lead	Blood lead and children
Lowozero (April 1995)	47, V	Serum Blood	Ferritin Lead	Blood lead and children
Kraschnochelie (April 1995)	14, V	Serum, Blood	Ferritin Lead	Blood lead and children

Nikel and Monchegorsk were selected because of the nickel refining operations located close to the city centres. Arkhangelsk is the biggest city on the White Sea, with five pulp and paper plants, but no metal producing industry. Kirkenes is located near the Russian-Norwegian border, 50 km from Nikel, receiving delivering women from the eastern part of Finnmark. Hammerfest, a coastal city of the western part of Finnmark, receives delivering women also from the largest Sami communities of Finnmark. Bergen is almost at the same latitude as Arkhangelsk, and is located in the south-western part of Norway; it has no metal producing nor heavy industry. It was included as a subarctic, Norwegian, urban community, outside the Barents Region. The total number of participants varied between the individual papers because of difficulties at different stages in sampling, transportation and analytical procedures, explained in the individual papers.

Table 2 summarizes the specimens collected, the analyses conducted, some details about the methods, and DLs of the employed methodologies. Further details about QA/QC-protocols and other analytical details are provided in the individual papers.

Table 2. Specimens collected, analyses conducted and details about methods and DLs of the methodologies used in the study.

Paper	Specimen	Analyses	Methods	DLs
I	Maternal urine and newborn`s urine	Nickel	Electrothermal atomic absorption spectrometry	10 nmol/L
		Creatinine	Spectrophotometry (Beckham Creatinine Analyser based on Jaffe's reaction)	0.01 mmol/L
II	Maternal serum	Copper and Zinc	Flame atomic absorption spectrometry, applying microcup technique	0.08 μmol/L 0.1 μmol/L
		Selenium	Electrothermal atomic absorption spectrometry	0.04 μmol/L
		Ferritin	Chemiluminoscence (Hitachi 917 autoanalyzer)	
III	Maternal blood and cord blood	Cadmium Lead	Electrothermal atomic absorption spetrometry	1.0 nmol/L 0.02 μmol/L
IV	Maternal urine and newborn`s urine, maternal serum and blood, and cord blood	Nickel Creatinine Copper Ferritin Selenium Zinc Cadmium Lead	See above	See above
V	Child`s serum and blood	Ferritin Lead	See above	See above

The statistical approach was based on univariate analysis, analysis of variance and multiple linear regression analysis, and are described in the individual papers. An association was accepted when the 95 % confidence interval (CI) of the regression coefficient did not include zero. In general, the essential elements showed a homogenous distribution pattern, while the toxic metals were highly skewed. Concentrations below the detection limit (DL) were arbitrarily assigned the value of ½ DL. The birth weight outcome or the body mass index of the child (BMIC) were employed as continous variables. Birth weights and BMIC corresponding to gestational age <week 40 were adjusted based on the observed mean weight gain of 166 g/week in the gestational period 30-38. The following empirical formulas were used:

1. Adjusted birth weight in g = Birth weight + (166 x 39 – 166 x gestational age);
2. Adjusted BMIC in kg / m^2 = ((Birth weight/1000 + (0.166 x 39 – 0.166 x gestational age))/(child`s birth length$^2$/10 000); with birth weight in grams, gestational age in weeks, and child`s birth length in cm.

Other potential confounders were tested as variables in the multivariate analyses, including: smoking, nationality, mineral status, local food intake, pre-eclamptic condition, maternal age and maternal anthropometric parameters, parity and sex of the baby. Analysis of variance by quartiles were adjusted for nationality (the «country factor»).

MAIN RESULTS

Paper I

Urinary nickel concentrations and selected pregnancy outcomes.

Urinary nickel concentrations in delivering women and their newborns in the Russian communities were measured and compared with Norwegian levels, and birthweight and BMIC were assessed in relation to urinary nickel concentrations and questionnaire-based anamnestic information. Urinary nickel excretion was significantly higher in the Russian communities, independent of the presence of a nickel refinery as a local environmental source. Birthweight and BMIC were significantly lower ($p<0.001$) in the Russian groups, with or without adjustment for gestational age. The multivariate linear-regression analysis indicated that maternal urinary nickel concentration had no impact on birth weight. Maternal body mass index (BMI) and maternal height were positive explanatory variables; maternal urinary creatinine is suggested as a weak negative factor. Smoking was shown to be a strong negative predictor only in the Norwegian group among whom there was a significantly higher smoking frequency ($p=0.005$). The significant contribution of a country factor in the predictive model indicated that important risk factors for low birth weight or BMIC were not identified.

Paper II

Essential elements, birth weight and newborn body mass index.

Delivering women and their newborns were studied to explore a relationship between maternal status of essential elemnts and birth weight or BMIC. Life-style information and serum specimens were collected from the selected Russian and Norwegian study groups. Pregnancy outcomes were verified by consulting medical records. Copper, selenium, zinc and ferritin in serum were determined. Mean birth weight as well as BMIC were significantly lower in the Russian group ($p<0.001$). Copper, iron (as ferritin) and selenium serum concentrations were in the normal range, while zinc levels in both countries were mostly below the lower limit of the suggested end of pregnancy interval. The combined results of univariate or multivariate regression analyses for birth weight or BMIC suggested the following associations: Serum zinc was a positive predictor at concentrations exceeding 10.8 µmol/L. The influence of the different elements on BMIC, grouped by quartiles, was significantly positive only for selenium ($p=0.03$) and ferritin ($p=0.02$), while there was no signficant relationship for copper or zinc. In the same manner, maternal urinary creatinine concentration and birth weight were negatively correlated ($p=0.001$). With the exception of zinc, the mineral status of delivering women in arctic and sub-arctic regions of Norway and western Russia appears to be adequate. However, the significant lower BMIC for the Russian group suggests that there might be nutritional deficiencies during pregnancy in Russia, but the trace elements explored in this study did not give any explanation for this suggestion.

Paper III

Blood lead and cadmium and birth weight.

Delivering women and their newborns in the selected study areas of Russia and Norway were studied to explore relationships between maternal cadmium and lead status and birth weight as a pregnancy outcome. Lead and cadmium were determined in the blood samples. The median cadmium value for the Russian group was 2.2 nmol/L ($N=148$) versus 1.8 nmol/L in the Norwegian group ($N=114$), $p=0.55$. A weak association was observed between maternal cadmium and amount smoked ($r=0.30$, $p<0.001$); no correlation was found between maternal blood cadmium and birth weight. The corresponding lead values were 0.14 (Russia) and 0.06 µmol/L (Norway), $p<0.001$. The median Norwegian lead concentration constitutes one of the lowest adult population values reported to date. Maternal and cord blood lead levels were strongly correlated ($r= 0.88$, $p<0.001$). In the multivariate linear regression model, maternal blood lead was recognized as a negative explanatory variable ($p<0.05$) for birth weight and BMIC, with or without adjustment for gestational age. A similar association was suggested by ANOVA-analysis of maternal blood lead by quartiles. Maternal blood-lead level as an environmental factor seems to be an apparent predictor of low birth weight and BMIC. It reduced substantially the contribution of a country factor in explaining the observed differences in birth weight.

Paper IV

Selfreported ethnic status, newborn body mass index, and blood, serum or urine concentrations of toxic and essential elements.

As part of the Arctic Monitoring and Assessment Programme (AMAP), we assessed pregnancy outcome among the Sami and Norwegian populations of Finnmark County in Norway and Russians living in the Kola Peninsula of Russia using BMIC as the main indicator. Concentrations of essential and toxic elements in biological fluids of the participants served as additional sources of information. At the hospitals of Hammerfest and Kirkenes in the period November 1993 - June 1994, a total of 107 consecutive women gave birth to a child, of whom 15 regarded themselves as Sami. The Russian group (N=151) delivered their children in the same period. The Sami women were significantly older than the Russian group (28.5 versus 25.1 years, $p=0.04$). The mean birth weight was significantly lower in the Sami group compared to non-Sami Norwegians ($p=0.01$), but was of comparable magnitude to that recorded in Russia ($p=0.4$). For BMIC, the Sami and Norwegian results were similar ($p=0.2$); both were significantly higher than in Russia ($p<0.001$). The essential elements copper, zinc, selenium and iron (as ferritin) in serum showed no differences between the groups, although relatively low levels of serum zinc were documented in all populations studied. Blood cadmium concentrations were strongly related to smoking frequency. Blood lead and urinary nickel levels were significantly higher for the Russian mothers, but did not reach levels of medical concern. No ethnic differences in concentrations of essential elements in biological fluids, nor of cadmium and mercury were observed. However, national differences for lead and nickel were evident. These conclusions must be discussed with caution because of the small numbers in the study groups. The similar BMIC values observed for the Norwegian and Sami newborns, compared to the Russian groups, suggest that BMIC may serve as a good indicator of the nutritional status and possibly also the general health condition of neonates.

Paper V

Elevated blood lead concentrations in children living in isolated communities of the Kola Peninsula.

On request by the Murmansk health administration, lead levels were determined in children aged 5-14 in three communities: two groups (N=24 and 39) from Apatity, an industrial town; a group (N=47) from Lowozero, an isolated Saami village; and another (N=14) from Krashnochelie, a remote native village with Sami, Komi and Nenets populations. Unexpectedly high blood lead concentrations were found in the most isolated community, namely Krashnochelie. The median lead concentration in Krashnochelie was significantly higher ($p<0.01$ or $p<0.02$) than those for Lowozero and Apatity. In the Krashnochelie group, the lead levels were not gender dependent. The percentage of children with blood lead concentrations at or above the medical concern level of 0.48 μmol/L was highest (36 %) in Krashnochelie, compared to 4.2 and 9.8 % in the two groups of Apatity and 6 % in Lowozero. All but three of the 124 individuals tested had ferritin concentrations above that indicative of depleted iron stores (10 μg/L for age <14 years); the median ferritin values were comparable for all four communities. Iron status differences can therefore not explain the elevation of blood lead concentrations in the Krashnochelie group. One probable explanation for the high lead concentrations is the use of leaded ammunition in subsistence hunting.

Paper VI

Critical evaluation of medical, statistical and occupational data sources in the Kola Peninsula.

A feasibility study of occupational exposed workers in the nickel industry of Kola Peninsula was prompted by a first report in 1992 of possible reproductive and developmental health concerns among female workers in a Russian nickel refinery. The primary goal of the study was to ascertain whether medical, statistical and occupational databases could be accessed for information about the pregnancy histories, occupational histories and life-style factors of the women affected. The project was facilitated by constructing a birth registry of all births in three towns with a nickel refinery and verifying its contents against patient records obtained from hospital delivery and gynecological departments and community polyclinics. Municipal Registration Board, Regional Health Statistics Board and nickel company records were also reviewed. The study showed that reproductive/developmental outcome information and workplace histories were acceptable. Sample-size calculations indicated that a cohort study would be amenable and suitable to detect an excess risk of spontaneous abortions with adequate statistical significance and power. Such investigations must be supplemented by workplace environmental/biological monitoring assessments to assess exposure to occupational hazardous factors and a worker's questionnaire to obtain information about life-style factors. A nested case-control design in the Kola Birth Registry is recommended for studying congenital defects. The Feasibility Study indicated that a well-designed, comprehensive epidemiological study is possible because of the availability of a favourable pool of study subjects, reproductive/developmental outcome data, information to control for major confounders, and suitable occupational records.

DISCUSSION

A Summary of Major Findings

(a) The mean birth weight and BMIC were statistically significant lower in Russian neonates.

(b) Urinary nickel concentrations were statistically significant higher in Russian mothers and neonates.

(c) Blood lead concentrations were statistically significant higher in Russian mothers and neonates. The Norwegian maternal and neonatal lead concentrations constitute some of the lowest values reported to date.

(d) The mineral status of delivering women in arctic and sub-arctic areas of Norway and western Russia seems to be adequate, with the exception of zinc.

(e) The univariate and multivariate linear regression models tested, when supplemented by analysis of variance by quartiles, have shown that maternal blood lead concentrations, maternal urinary creatinine concentrations, and smoking impact negatively on birth weight or BMIC; maternal serum zinc, selenium and ferritin appear to have weak positive influences. Anthropometric explanatory factors that were positively correlated were maternal BMI, height and weight, as well as parity and maternal age. Adjustment for gestational age did not alter these conclusions.

(f) There were no ethnic differences in concentrations of essential and toxic elements in body fluids.

(g) Blood lead concentrations in schoolchildren living in remote areas of the Kola Peninsula were high, up to the level of medical concern.

(h) The Kola Birth Registry was set up as a research and public health tool. As a practical result of our work, the Federal Government of Russia is preparing a simplified version of the Kola Birth Registry for use in all counties of the Russian Federation.

(i) A well-designed, comprehensive epidemiologic study of reproductive and developmental health among Russian nickel refinery workers is warranted, technically feasible and ongoing.

Limitations of the Reported Research

Information biases

Answers concerning the consumption of local food were not provided in the Russian community of Monchegorsk. The reason for this may reflect the decision by the local interviewer not to emphasize this component. The refusal by 36 % of the Russian respondents to provide information about alcohol consumption suggests that this topic is culturally sensitive. Interestingly, Stoler et al. (1998) conclude that maternal blood markers such as whole-blood associated acetaldehyde, γ-glutamyl-peptidase, or carbohydrate-deficient transferrin are more predictive of infant outcome from at-risk pregnant women than self-reporting methods, and that these markers might lead to better efforts to detect and prevent alcohol-induced fetal damage. This approach might have been useful in our study, since the self-reported alcohol consumption gave poor results. Even fewer individuals in Russia responded to educational background questions. Since education is a positive predictor of birth weight (e.g., Nordstrøm and Cnattingius 1996), its omission may have influenced the birth weight and BMIC analyses. Futhermore, dietary information sought through the questionnaire lacked specificity and was poorly answered. The use of this life style characteristic in the statistical analysis was therefore of limited validity and statistical power. Similarly, questions addressing sociodemographic details concerning economic status and employment were also weak.

Inconsistency between interviewers is a possible concern but unavoidable, since so many different communities were involved. Further, the questionnaire was translated from Norwegian into Russian and this may have had a steering effect on some of the questions. Of course, inherent ambiguities in the questions may have influenced the consistency of the answers. On the other side, the discrepancies between Norwegian and Russian physicians in classifying pregnancy complications and outcomes were minimal (Paper VI). An example is the diagnosis of the pre-eclamptic condition, which was defined due to strict, common criteria in both countries.

One factor not included in the statistical analyses was the risk of repeating low birth weight. Raine et al. (1994) have shown that prior delivery of a preterm low birth weight infant was a strong predictor of low birth weigh in a subsequent pregnancy, despite adequate prenatal care. Information about any previous births of under-sized babies was not collected, although our results were adjusted for parity. Specifics about the father such as weight and height were not solicited and thus could not be included in the multivariate analyses as independent variables.

Selection biases

Selection bias might have occurred for two reasons, namely transfer of cases with complications to regional hospitals and the exclusion from the statistical treatment of mothers and their neonates because of the unavailability of neonatal urine samples. Patient transfers were few and were registered. Inclusion of the neonatal weights for those without urinary nickel samples only reduced the difference between the Russian and Norwegian birth-weight means by 4 grams, which did not affect the significance test ($p<0.001$).

Confounders

Although many explanatory variables of birth weight were examined, others are known as discussed in the Introduction, such as paternal influence, maternal education, dietary factors, socioeconomic status and job stress. These characteristics could not be included in the multivariate modelling since the appropriate information was not collected. Further, the ability of lead to diminish the importance of the «country factor» in the multivariate analysis may constitute a surrogate-confounder effect, since the total lead data base is split into distinct groups by nationality. The mean maternal blood lead concentrations were 0.14 µmol/L (range 0.04-0.65) in Russia, compared to 0.06 µmol/L (range 0.02-0.19) for Norway. However, it is encouraging that the impact of lead on birth weight grouped by quartiles manifests itself most strongly in Russia, approaching significance. The view that the lead surrogacy is unlikely is further strengthened by the finding that the negative association between MBPb and BMIC (grouped by quartiles) only reached significance for the Russian study groups.

Sample size

Due to logistical and technical limitations, as well as economic restrictions, the sample size for each country was too small to detect differences in the incidence of congenital defects. Much larger populations need to be examined to identify such outcomes with adequate statistical power, as they are relatively rare (see Paper VI). The small number of cases identified in the present study is consistent with this.

Inadvertent contamination

Although we made every effort to minimize external contamination of the samples, the lack of opportunity to be personally involved in the early stages of the sample history (i.e., collection, handling, storage and transport to the laboratory) limited our ability to control the contamination risk. This may account for some of the outliers corresponding to the highest urinary nickel concentrations or maternal lead concentrations.

Explanatory Variables of Birth Weight and BMIC

Urinary nickel

The high urinary nickel concentrations found in the Russian mothers and neonates could not be explained by known point sources such as the nickel refineries (Paper I). This finding was confirmed in the Norwegian-Russian Health Study 1994/95 for males and females of the general population in the Kola Peninsula (Smith-Sivertsen et al. 1997; 1998). Smith-Sivertsen et al. (1998) have also explored differences related to age and sex, showing that urinary nickel tends to decrease with increasing age, with no significant differences related to sex. Smoking frequency had no effect.

The absence of an impact of nickel on birth weight and BMIC is consistent with the lack of health effects found in the cross-sectional population-based health studies constituting the Norwegian-Russian Health Study (Smith-Sivertsen et al. 1997). Russian women had a lower prevalence of nickel allergy, while men had the same prevalence in the two countries. Ear pearcing was demonstrated to be a strong risk factor for nickel allergy, while no conclusions could be made about the role of air pollution as a risk factor, despite the higher prevalence of inhalent allergy on the Russian side as measured by serum IgE concentrations. It was also concluded that lung function was better than predicted in both countries, and no clear associations between daily changes in sulphur dioxide and lung function could be verified.

Nickel concentrations in first-voided urines of neonates (Paper I) have not been reported previously. The significantly higher values for the Russian neonates suggest a free-flow of nickel across the placenta barrier, even though a strict relationship between maternal and neonatal urinary nickel was not observed.

The higher urinary nickel levels on the Russian side, independent of proximity to the nickel refineries, imply the existence of other sources than environmental pollution. Clearly nickel in tap water can account for only part of the higher creatinine-adjusted urinary nickel levels found in Nikel and Monchegorsk (Paper I), since median tap water nickel levels in other Russian communties were comparable to those found in the Norwegian locations. Suggested sources have been certain food stuffs, like cocoa, nuts, dried legumes and certain grains (Nielsen 1992). Leaching into drinking water from nickel-plated plumbing or from cooking utensils, as well as oral prosthesis have been suggested (Nieboer et al. 1997). A comprehensive dietary study seems appropriate to explore this issue. This dimension will need to be implemented among control subjects of the planned, reproductive-health cohort study of female workers of the Monchegorsk nickel refinery (Paper VI). As reported in Paper I (also see Thomassen et al. 1999), female nickel workers experienced considerably higher nickel and cobalt exposures and intakes than non-nickel workers judging by the observed urinary nickel concentrations.

Urinary creatinine

The inadvertent finding of a negative correlation between maternal urinary creatinine and birthweight (Paper I) might be interpreted as a manifestation of subclinical pre-eclamptic pathohysiology. Endothelial injury in the general circulation has been postulated to incur renal damage, including oliguria (Erkkola 1997). The observed creatininuria might therefore reflect the significantly higher incidence of pre-eclampsia in the Russian women (Papers I, II, and III). It is clear that the pre-eclamptic process enhances the risk of perinatal morbidity, including low birth weight (Erkkola 1997), although an association between pre-eclampsia and birth weight could not be established in our study. Briefly, a process is initiated that through many steps leads to hypoperfusion and local hypoxia, disturbing the functioning of placental endothelial cells. Baker and Hackett (1994) discuss early predictors of endothelial damage, using enhanced urinary albumin-creatinine ratios and reduced calcium-creatinine ratios as screening tests for pregnancy-induced hypertension (also see Grunewald 1997). Increased urinary creatinine concentrations were indeed found in patients who subsequently developed pregnancy-induced hypertension (Baker and Hackett 1994). It is not clear whether oliguria alone accounts for the increased urinary creatinine concentrations. Osmolality measurements would help to resolve this issue.

In our study we have used spot specimens of maternal and child`s urine, unadjusted or adjusted for creatinine. Our assessment of birth weight and BMIC show only minor changes when the adjusted values are employed. Sunderman et al. (1986a, b) recommend that 24-hour specimens be collected to minimize dilution effects. However, this is impracticable in our type of study. Nieboer et al. (1992) concluded, in a study of Canadian nickel workers, that specific gravity adjustment of nickel concentrations in spot samples when combined with appropriate lower and upper limits constitutes the most suitable correction. Although specific gravity would therefore appear to be preferred over creatinine, it was not feasible to include this measure in our Russian sampling protocol. The lower neonatal creatinine-adjusted nickel levels compared to maternal values might be expected due to the lower GFR at birth (20 % of adult values) (Ichikawa 1990). Neonatal creatinine excretion during the first week after birth has been correlated with muscle mass (Modi and Hutton 1990), which supports our finding of a week relationship between creatinine concentration in urine and birth weight (Paper I).

Mineral status

Generally, our results for the various elemental concentrations measured fall into accepted intervals (Minoia et al. 1990; Burtis and Ashwood 1994). An important exception is the lower mean serum zinc concentrations in arctic areas, compared to the sub-arctic group of Bergen and available reference intervals. The unusually wide range of the ferritin levels in both countries is also noteworthy. High ferritin has been associated with early spontaneous premature delivery (Tamura et al. 1996). There is no obvious explanation for the lower serum zinc concentrations in the arctic areas. In a Scandinavian double-blind randomized-controlled trial, Jønsson et al. (1996) could not show any significant increase in serum zinc levels in a group receiving zinc-supplementation during pregnancy. However, positive responses to supplementation have been reported by others (Neggers et al. 1991; Goldenberg et al. 1995).

Other than zinc, the status of copper, iron, or selenium seems satisfactory. This finding is rather surprising because of: the routine supplementation (especially iron) of pregnant women in Norway and other western countries; the perception that poor dietary conditions prevail in Russia; and the significant differences in BMIC found.

The positive correlation found in our study between zinc and birthweight for zinc concentrations exceeding 10.8 μmol/L concurs with the suggestion of a treshold below which a risk for low birth weight seems to occur (Neggers et al. 1990). The positive correlations found between selenium and ferritin and BMIC, like that for zinc and birth weight, highlight the importance of good nutrition during pregnancy.

Obviously, important aspects of dietary influence on pregnancy are not explored with the small selection of essential elements examined in this study. Nevertheless, it seems prudent to conduct additional research to explore the low serum zinc levels found in the delivering women, as well as possible dietary contributions to the observed difference in BMIC. The administration of a detailed food questionnaire would be necessary.

Smoking and cadmium

Cadmium concentrations in all areas were low, although they correlated with smoking habits. The insignificant impact observed of cadmium on birth weight and BMIC finds support in the work by Loicano et al. (1992). After controlling for confounding variables, they found no association between placental cadmium and birthweight and the effect of smoking appeared not to be mediated through cadmium. The relatively low smoking frequency observed , especially in Russia, probably accounts for the result that smoking only occurred as a negative predictor of birth weight in the univariate analysis for the Norwegian group and was not retained in the multivariate analysis that included essential and toxic elements as parameters. Interestingly, recent Russian figures for the years after our field work are very discouraging, showing that the smoking freqency in Russian pregnant populations now approach those reported for the Norwegian study group (Nieboer et al. 1997).

Blood lead

The Norwegian blood lead concentrations constitute some of the lowest reported to date. Even so, a significant negative impact on birth weight and BMIC was observed in the multivariate model. As already indicated (see Limitations section), elimination of the «country factor» as a significant variable in the model when maternal lead was included, is likely a real effect. This finding is strengthened futher when adjustment for gestational age was made.

Andrews et al. (1994) have reviewed all epidemiological studies on prenatal lead exposure. They concluded that associations between prenatal lead exposure and premature rupture of membranes (PROM), preterm delivery or gestational age have not been confirmed, although the existing literature does support a relationship between prenatal lead exposure and birthweight. In fact, this relationship appears to have a treshold.

The correlation observed between maternal blood lead and cord blood lead is very strong ($r=0.88$, $p<0.001$), verifying that free transfer of lead occurs through the placenta barrier (Hubermont et al. 1978).

Anthropometric measurements

The Norwegian women were somewhat heavier than the Russian mothers in our study (not significant), and taller ($p<0.001$), but the mean BMIs were practically identical ($p=0.7$). Interestingly, the exclusion of maternal height from the multivariate analyses results in a significant loss of information. This was not the case for maternal weight, presumably because it is adequately represented in BMI. The positive contribution of BMI and maternal height in explaining birth weight or BMIC seemed to be strengthened by gestational age adjustments. As already indicated (see Introduction), the effect of maternal size on birth weight and BMIC is most likely mediated through constitutional and genetic factors rather than in utero nutrition (Mongelli et al. 1996).

Birth weight and BMIC as pregnancy outcomes

The similar BMIC values observed for the Norwegian and Sami newborns, compared to the Russian groups, suggest that BMIC may serve as a good indicator of the nutritional status and possibly also the general health condition of neonates (Paper IV). However, we could not prove that BMIC is a better measure of neonatal welfare than birth weight. Based on the essential elements considered, the view that BMIC better reflects intra-uterine nutrition (e.g., Wandja et al. 1995) is not borne out. Our results suggest that these two indices provide complementary information. A similar conclusion appears to hold for other indices of neonatal health. In the present study, the multiple regression models gave exactly the same results when BMIC or Ponderal Index (weight/(length)^3 in kg/m^3) was selected as the dependent variable.

Cole et al. (1997) discuss the usefulness of birth weight versus BMIC, Ponderal Index or Benn Index (child's birth weight/(length)^n in neonatal assessment. Past 39 weeks gestation, the Ponderal Index is negatively correlated with length, while the BMIC is uncorrelated, suggesting that BMIC is better. Of these quantities, the Benn Index is the most general as it assigns the most suitable value of n, the power of length, for each week of gestation. The Ponderal index seems not appropriate for measuring intra-uterine malnutrition, while BMIC is a precise tool for evaluation of the birth weight for length at term and thus neonatal general well-being.

Gender differences in birth weight, BMIC and Ponderal Index have been discussed by Guihard-Costa et al. (1997). The male neonates usually have higher birth weight and BMIC values than girls (a fact which was not observed in the present study), with the Ponderal index showing no sexual dependence.

Wilcox et al. (1995) have introduced a new analytical approach based on relative birth weight. A comparison of linked birth and perinatal death records for US and Norwegian births from 1986 through 1987 was performed. The outcome measure was defined as perinatal weight-specific mortality after adjustment for country. The study demonstrated that prevention of increased perinatal mortality depends on the prevention of preterm births, not on changes in mean birth weight. Our study is far too small to detect changes in perinatal mortality, with only one perinatal death during the sampling period (a child with hydrocephalus in Arkhangelsk).

Our study population consisted of consecutively born children in each geographical area; with 11 Russian children (week 30-35) and 2 Norwegian children (week 32-35) below gestational age 36. Relevant adjustments were included in the statistical assessment. We observed a limited linear relation between birth weight and gestational age up to week 39 of gestation, beyond which there was no systematic dependence. Showstack et al. (1984) also observed a non-linear relationship. A similar finding has been reported by Cogswell and Yip (1995), who found that gestational age only affects the low end of the birth weight distribution. Most other factors, like maternal race, infant sex, parity, education and smoking seem to affect the entire birth weight distribution, indicating a generalized effect. Cogswell and Yip (1995) also discussed the possibility that wide variation in birth weight at the high end of the scale may imply increased risk of morbidity or mortality; higher birth weight does not always equal better birth outcomes as explored in the next paragraph.

The proportion of children with high birth weights appears to have increased in all Nordic countries in recent years (Medical Birth Registry of Norway 1995; Meeuwisse and Olausson 1998). In Sweden, the proportion of offspring at term (>36 gestational weeks), weighing 4 kg or more increased from 16.9 % in 1973 to 20.3 % in 1995. The mean birth weight increased from 3400 to 3520 g. There was a corresponding increase in head circumference. A higher risk of delivery-related complications has been demonstrated, like major perineal rupture, as well as brachial plexus damage. Meuwisse and Olausson (1998) suggest that the higher birth weight is associated with an increased risk of subsequent morbidity, both in childhood and adulthood; specifically, Type 1 diabetes, eczema, and certain malignancies, particularly breast cancer and prostate cancer. The cause of the increasing proportion of large newborns is not clear, but might be associated with increasing maternal weight, probably due to dietary changes, or reduced maternal smoking. It might be interesting to repeat our study if the socio-economic conditions in Russia improve. However, the smoking frequency of Russian pregnant women has increased since our field work was conducted (Murmansk Regional Health Administration 1998). By contrast, a recent Swedish/Czech study (Koupilova et al. 1998) demonstrates a general fall in mean birth weight and increasing dependence of birth outcome on social status in the Czech Republic, a finding not seen in the Swedish reference group. This result was interpreted to reflect the decline and divergence in living standards in the Czech Republic during 1989-91. As discussed in a subsequent section (The Kola Birth Registry), similar trends appears to have taken place in the Kola Peninsula.

The mean BMIC observed compares well with values reported for India. Bhalla and Walia (1996) found the mean BMIC in a geographical area of the Punjab to be 12.2 (male) and 12.5 kg/m^2 (female), close to the mean value of 11.9 kg/m^2 in our Russian study group (compared to 14.0 kg/m^2 in the Norwegian group and 13.5 in the Sami sub-group; Paper IV). In a more developed part of India, birth weight has been shown to increase and the percentage of low birth weight has declined, especially in the rural communities. Interestingly, the rural newborns weighed less than their urban counterparts (Antonisamy et al. 1994).

Occupational and educational aspects

Our study of pregnant women was not designed to detect developmental and reproductive problems in occupationally exposed population groups. Sample size was the limitation. An interesting aspect is the relatively high mean birth weight (3342 g, N=9, Paper I) of the economically privileged, but occupationally exposed workers in the Monchegorsk nickel electrorefinery. We could not detect differences in mean birth weight or BMIC between groups of different self-reported occupations, which included non-employed women and women with strenous working conditions (data not shown). Thus we could not confirm the observation by Bjerkedal et al. (1980) that pregnancy complications were higher among births of economically active mothers and that industrially employed mothers were at highest risk. Of course, the small sample-size may be the reason. Strenous working conditions have been specifically connected to increased incidence of pre-eclampsia (Wergeland and Strand 1997). Since female employment in Russia is high in industrial settings normally reserved for men in western countries (e.g., construction, mining, and metal refining in the Kola Peninsula, see Paper VI), maternal occupation may well have contributed to the high prevalence of pre-eclampsia found. The stress level of working women may also be enhanced by the lack of male participation in domestic chores.

As already indicated, information about the educational level of the Russian women was incomplete in our study. In the Norwegian group a positive, but insignificant, correlation occurred between years of education and birthweight (β-coefficient 15.5; 95 % CI -9.1, 40; $p>0.05$).

Sami as a Sub-population

In Paper IV, we were not able to demonstrate any differences in biological concentrations of essential or toxic elements between the self-reported Sami study subjects and the Norwegian mother/child pairs. Although Sami neonates were lighter, approaching that of the Russian newborns, the BMIC concurred with the Norwegian data.

There are many difficulties in the definition of ethnic status for scientific purposes (Ahdieh et al. 1996) and therefore self-reported ethnic status was employed. Interestingly, Lahermo et al. (1996) have shown Finnish Sami to be genetically distinct, a finding that likely applies to the Norwegian Sami as well. As reviewed in the Introduction, genetic factors can influence birth weight and this is relevant clinically when defining large-for-gestational age infants in diabetic pregnancies (Dornhorst et al. 1996). Our observations concerning the Sami mother/neonate pairs cannot be conclusive because of the small sample size, although they do warrant closer scrutiny and follow-up.

Lead in Children

A surprising finding in Paper V is that the highest blood lead levels in school children occurred in the most remote and isolated community. We would expect the Russian urban centers to experience greater lead contamination from leaded gasoline and industrial activities. A likely explanation is the higher consumption of traditional foods obtained in subsistence hunting with leaded ammunition (see Paper V for details). This interpretation has recently been confirmed in the work by Dewailly et al. (pers. com.), who used lead isotopes for tracing the source of the lead in native and non-native Canadians. The lead in the blood of native people could be clearly linked to the unique isotopic ratio characteristic of leaded ammunition.

As discussed in the Introduction, the blood-lead level of medical concern for children is not well-defined and that likely there is no treshold level (e.g., Schwartz and Otto 1991; Todd et al. 1996). Both mild cognitive and behavioural symptoms are likely at the measured concentration levels. Lead intake advisories, rather than medical intervention or screening, are warranted. However, this approach will likely be complicated by the economic hardships that continue to occur in the Kola Peninsula. Dietary insufficiency is a known risk factor for enhanced lead absorption (Mahaffy 1990; Sargent 1994).

The Kola Birth Registry

The construction of the Kola Birth Registry was a response to the concern expressed by Chashschin et al. (1994) about a possible increase in structural malformations among babies of occupationally-exposed female nickel workers (see Paper VI). The possibility of initiating a comprehensive epidemiologic study of the reproductive health among female nickel workers was confirmed by a Feasibility Study (Nieboer et al. 1997; Paper VI). A high priority for this work was a birth registry constructed following international guidelines.

To date, the Kola Birth Registry includes 12 560 maternal/neonatal entries. By the end of 1997, its 4750 entries covered births for the years 1986-1993 for the towns of Nikel, Zapolyarnyi and Monchegorsk. Since that time the original entries have been checked and verified against the original medical records and all births for the years 1973-76, 1983-85, and 1994-96 have been added for Monchegorsk. About 40 % of the registered adult females work at Severonickel, of whom about one-half are extensively exposed (mostly to nickel).

Information about childhood illnesses have been added up to 15 years of age. To compile data on centres in the Kola Peninsula without heavy industry, births from the town of Lowozero are being added. Many of the inhabitants of this town are indigenous people (see Paper V). The usefulness of the Kola Birth Registry is becoming evident. For example, the trends in birth rate, stillbirths, perinatal deaths and birth weight for the years 1981-93 for the entries are compared in Table 3 with the national Norwegian statistics. A perusal of the numbers show a moderate increase in birth rates in Norway, and a dramatic decline in Russia in the period

1988-1993 (end of the «Perestroika effect»). The economic conditions may also make pregnancy less common among low income women, as reported for the Czech Republic (Koupilova et al. 1998). The trend to lower perinatal death cases in Norway appear to be weakly reflected in the Kola statistics. While the mean birth weight in Norway has remained nearly constant over the period considered, there is a slight downward trend in the Kola Peninsula, which is consistent with the worsening of the economic conditions.

Another use of the Birth Registry is to examine the prevalence of childhood cancers. Preliminary results suggest an enhanced risk for babies born in Monchegorsk, especially of parents employed in nickel refining. In the next section, the possibility of a nested-case-control study of birth defects within the Birth Registry is described.

Russian health officials have aknowledged the importance of the Birth Registry as a public health research and monitoring tool. The Federal Health Ministry of the Russian Federation is considering the adoption of a simplified version of the Kola Birth Registry for use in all counties of the Russian Federation.

Table 3. Examples of trends in birth rate, stillbirths, perinatal deaths, and birth weight, adapted from the Norwegian Birth Registry and the Kola Birth Registry for the period 1981-93.

Year	Birth rate (per 1000)		Perinatal deaths (per 1000)		Birth Weight (mean, grams)	
	Norway	Kola	Norway	Kola	Norway	Kola
81	11.9	17.4	9.5		3499	
82	12.0	18.0	10.0		3488	
83	11.7	20.0	10.2		3484	3303
84	11.8	19.3	8.9		3485	3367
85	12.0	18.8	9.3	21.1	3478	3362
86	12.3	19.2	8.1	23.4	3486	
87	12.7	19.6	7.9	27.2	3481	
88	13.5	16.3	8.0	21.9	3482	3379
89	13.9	13.3	7.7	19.8	3478	3440
90	14.3	12.0	7.7	21.3	3474	3340
91	14.0	10.0	7.1	20.1	3477	3333
92	14.1	8.3	7.1	13.2	3490	3235
93	14.0	8.4	6.8	18.0	3509	3245

Reproductive Study of Nickel Workers

As indicated in Paper VI, a preliminary report of raw data about apparent increases in spontaneous abortions among female nickel workers and structural malformations in their babies was published by Chaschschin et al. (1994). The Feasibility Study of Reproductive and Developmental Health in Relation to Occupational Exposure to Nickel in the Kola Peninsula of Russia (Nieboer et al. 1997) was initiated to determine if a more comprehensive epidemiologic study was possible. The Feasibility Study included exposure assessments by personal sampling, and an evaluation of the availability and reliability of medical registers, records, and journals. A worker questionnaire exploring life-style and other personal issues was also tested among the female nickel workers. The exposure assessment clearly showed that the Monchegorsk nickel workers are heavily exposed to nickel-containing process intermediates (Thomassen et al. 1999). It was concluded that a well-designed, comprehensive epidemiologic study is technically feasible because of the availability of a favourable pool of study subjects, reproductive/developmental outcome data, information to control for major confounders, and suitable occupational records. Current exposure assessments may be expected to reflect past exposures as few process changes in the refining of nickel have been made in the period 1970-present.

A consideration of the size of the past and current workforces of the Monchegorsk refinery and sample size calculations indicated that a cohort study of all pregnancies since 1970, or a cross-sectional study of pregnancies among current workers, would be amenable and suitable for the detection of an excess risk of spontaneous abortion with adequate statistical significance and power (see Paper VI). Exposure assessment by job categories supplemented by biological monitoring are also required to explore causal relationships. A questionnaire seeking life-style information pertinent to reproductive health needs to be administered. A case-control study of birth defects nested within the Kola Registry appears to provide a valid approach to detect and explore adverse developmental outcomes.

The described studies are in progress.

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Резюме

Предпосылки

Исследование началось из-за страха общественности перед неблагоприятными явлениями в репродуктивном здоровье и исходах беременности в районе русско-норвежской границы по соседству с никель производящей промышленностью на Кольском полуострове. Первоначальной задачей было оценить состояние здоровья рожающих женщин и результат их родов среди обычного населения русско-норвежской арктической территории, включая также оценку концентрации жизненно-необходимых и токсичных элементов. В ходе исследования важной проблемой стало также здоровье женщин-рабочих никелевой промышленности, подвергающихся профессиональной экспозиции, и детей, живущих на Кольском полуострове. *Материал*: В период с апреля 1994 по июнь 1994 года была собрана информация приблизительно о 50 матерях, об их родах, образцы их крови и мочи, а так же образцы крови и мочи их новорожденных детей из 3 городов России : Архангельска, Никеля и Мончегорска и из трех норвежских городов: Киркенеса, Хаммерфеста и Бергена. Архангельск был выбран как большой субарктический город без какой-либо никелевой промышленности, в то время как Никель и Мончегорск были включены как города с никелевой промышленностью. Киркенес был выбран как самый близкий по соседству к русской никелевой промышленности норвежский город, Хаммерфест как арктический город на побережье и Берген как другой субарктический город без какого-либо производства металла, и находящийся на почти той же самой широте, что и Архангельск. Кроме того, в 1995 году по просьбе местного здравохранения была собрана информация о детях и образцы их крови из индустриального города на Кольском полуострове – Апатиты, и из двух удаленных деревень с коренным населением: Ловозеро и Краснощелье. *Результаты*: Концентрация никеля в моче была значительно выше в русских исследуемых группах. Источники экспозиции никелем русского населения, которые могли бы объяснить это различие, остаются невыясненными. Экспозиция никелем, полученная из окружающей среды, оценивается по выделению никеля из мочи, и, как было показано, не является предсказывающей переменной ни для низкого веса при рождении, ни для показателя массы тела новорожденного (индекс BMIC). Минеральный статус рожениц из арктических и субарктических областей Норвегии и западной России был адекватный, кроме цинка. Различие в концентрациях цинка в русской и норвежской сыворотке указывает на различие между арктическими и субарктическими областями по разные стороны границы двух стран. Цинк в материнской сыворотке являлся позитивной предсказывающей переменной для веса при рождении. Свинец в материнской крови был негативной предсказывающей переменной для веса при рождении, даже при столь низких концентрациях. Включение в расчеты по многовариантной модели свинца в материнской крови привело к потере статистической значимости по неспефическому различию стран. Концентрация свинца в крови школьников, живущих в удаленных районах Кольского полуострова, доходит до уровня, требующем врачебного рассмотрения. Средний вес при рождении и показатели массы тела новорожденного (индекс BMIC) были значительно ниже в русских группах, вероятно, за счет дефицита в питании во время беременности в России. Врожденные уродства встречались слишком редко, чтобы их оценивать. Однако, это исследование не касается рассмотрения влияний на репродуктивное здоровье и на развитие плода как среди обычного населения, так и среди женщин с высокой экспозицией, работающих в русской никелевой промышленности. Рабочие Мончегорского никелевого комбината сильно эспонированы никелем, и занятость матерей на никелевом комбинате должна быть исследована в дальнейшем как фактор риска для вредных репродуктивных последствий. Хорошо спланированные, полные эпидемиологические исследования репродуктивного здоровья и развития плода среди рабочих никелевого комбината вполне возможны технически, гарантированы и уже проводятся. *Заключения*: Никакие влияния исследованных факторов загрязнения, за исключением отрицательного влияния концентраций свинца в материнской крови, не были замечены на последствия беременностей, на вес при рождении и на показатель массы тела новорожденного (индекс BMIC). Статистически значимое различие между средним норвежским и русским показателем массы тела новорожденного (индекс BMIC) предполагает, что в русских группах могло быть плохое питание матери во время беременности. Концентрации свинца в крови, по своему уровню приближающиеся к значению, требующему врачебного вмешательства, наблюдались у детей, живущих в удаленных местах Кольского полуострова.

Основные результаты

Статья I

Концентрация никеля в моче и возможные исходы беременности

Была измерена концентрация никеля в моче и проведено сравнение этих значений у рожающих женщин и их новорожденных детей в русских и норвежских областях, а также оценены вес при рождении и BMIC- критерий в связи с концентрацией никеля в моче и по анамнестическому опросу. Выделение никеля в моче было существенно выше в русских областях вне зависимости от того, был ли никелевый комбинат, являющийся источником загрязнения окружающей среды, в данной области или нет. Вес при рождении и BMIC критерий были существенно ниже в русских группах ($p<0.001$) как с корректировкой, так и без нее, на срок беременности. Многовариатный линейно-регрессионный анализ не показывает влияния концентрации никеля в моче на вес при рождении. Индекс материнской массы тела (BMI) и материнский рост были позитивно коррелированы с концентрацией никеля в моче; в то время как креатинин в моче, видимо, являлся незначительным отрицательным фактором. В то же время курение оказалось значительным отрицательным фактором только для норвежской группы, среди которой частота этой вредной привычки была значительно выше ($p=0.005$). Фактор страны в данной модели не был убедителен как важный фактор риска для веса при рождении или критерия BMIC.

Статья II

Жизненно-важные элементы, вес при рождении и индекс массы тела новорожденного

Рожающие женщины и их новорожденные дети были исследованы для того, чтобы изучить взаимосвязь между материнским статусом по жизненно-важным элементам и весом при рождении или BMIC. Была собрана информация об образе жизни и образцы сыворотки от русских и норвежских групп. Исходы беременности были проверены по медицинским картам. Были определены медь, селен, цинк и ферритин в сыворотке. Средний вес при рождении также, как и BMIC, были значительно ниже в русской группе ($p<0.001$). Медь, железо (в виде ферритина) и селен в сыворотке были в обычном диапозоне, тогда как уровень цинка для обеих стран был в большинстве своем ниже низшей границы диапазона, характерного для конца беременности. Комбинированные результаты единичного- или много-вариантного регрессионного анализа веса при рождении или BMIC показали следующее: цинк в сыворотке являлся позитивным предсказателем при концентрациях, превышающих 10.8 мкмоль/л. Влияние различных элементов на BMIC, сгруппированных по частоте распределения в четыре равных интервала, давало заметную корреляцию только для селена (p=0.03) и ферритина (p=0.02), в то время как никакой взаимосвязи не было для меди и цинка. Т.о., (негативно) отрицательно коррелируют между собой концентрация креатинина в материнской моче и вес при рождении (p=0.001). За исключением цинка, минеральный статус рожающих женщин в арктических и субарктических областях Норвегии и западной России, вероятно, является одинаковым. Вместе с тем, значительно более низкие значения BMIC в русской группе могут быть объяснены дефецитом в питании матерей в России во время беременности. Однако, исследование следов элементов, проведенное в этой работе, не дало какого-нибудь подтверждения этому предположению.

Статья III

Свинец и кадмий в крови и вес при рождении

Для того чтобы исследовать взаимосвязь между материнским статусом по кадмию и свинцу и весом при рождении, как исходом беременности, были изучены рожающие женщины и их новорожденные дети из нескольких районов России и Норвегии. Были определены свинец и кадмий в их крови. Значение медианы кадмия в русской группе состовляло 2.2 нмоль/л (N=148) против 1.8 нмоль/л в норвежской группы (N=114), p=0.55. Небольшая взаимосвязь наблюдалась между кадмием в материнской крови и количеством выкуренных сигарет (r=0.30, p<0.001); но не было никакой корреляции между кадмием в материнской крови и весом при рождении. Значения свинца были 0.14 (Россия) и 0.06 мкмоль/л (Норвегия), p<0.001. Медиана для свинца в норвежской группе является одним из самых низких значений для взрослого населения, о котором сообщается в данное время. Уровень материнской крови по свинцу сильно коррелирует с уровнем крови из пуповины (r= 0.88, p<0.001). В многоварнатной модели линейной регрессии, свинец в материнской крови был определен как отрицательная объясняющая переменная ($p<0.05$) для веса при рождении и для BMIC, с корректировкой и без нее на срок беременности. Подобную взаимосвязь предлагает и ANOVA- анализ свинца в образцах материнской крови, сгруппированных по частоте распределения в четыре равных интервала. Уровень свинца в материнской крови, по-видимому, в качестве фактора воздействия окружающей среды, может быть явным предсказателем низкого веса при рождении и низкого BMIC. Он существенно уменьшает вклад фактора страны при объяснении наблюдаемых различий в весе при рождении.

Статья IV

Собственная оценка этнического статуса, индекс массы тела новорожденных и концентрация токсичных и жизненно-необходимых элементов в крови, сыворотке и моче.

Как часть программы Арктического мониторинга и его оценки (AMAP), мы исследовали исход беременности среди населения саами и норвежского населения в Финмарке. Как в этой части Норвегии, так и на Кольском полуострове России пользуются в основном показателем BMIC. Дополнительными источниками информации к BMIC служили полученные концентрации жизненно-необходимых и токсичных элементов в биологических жидкостях участников этого исследования. В больницах Хаммерфеста и Киркенеса в период с ноября 1993 г. по июнь 1994 г. 107 женщин родили детей, из них 15 считали себя по национальности саами. В русской группе 151 женщина родили детей за тот же самый период. Женщины по национальности саами были значительно старше, чем в русской группе (28.5 против 25.1 лет $p=0.04$). Средний вес при рождении был значительно ниже в группе саами, чем в обычной норвежской группе ($p=0.01$), но был сравним по величине со значением в России ($p=0.4$). Для BMIC результаты саами и норвежские подобны ($p=0.2$); и оба значительно выше, чем в России ($p<0.001$). Жизненно-необходимые элементы медь, цинк, селен и железо (в виде ферритина) в сыворотке не различаются между группами, хотя относительно низкие уровни цинка в сыворотке были задокументированы для всех изученных групп. Концентрация кадмия в крови сильно связана с частотой курения. Уровень свинца в крови и никеля в моче был значительно выше у матерей из России, но тем не менее он не достигал уровня, при котором требуется вмешательство врачей. Никакой этнической разницы в концентрациях жизненно-необходимых элементов, а также кадмия и ртути в биологических жидкостях не наблюдалось. Однако, разница между нациями была очевидной по свинцу и никелю. Но эти выводы следует обсуждать с осторожностью из-за небольшого количества участников в группах. Аналогичные значения BMIC, наблюдаемые у норвежских новорожденных и новорожденных саами, при сравнении с русскими группами, указывают на то, что BMIC может служить хорошим индикатором статуса питания а, возможно, также индикатором общего состояния здоровья новорожденных.

Статья V

Повышенная концентрация свинца в крови детей, живущих в изолированных областях Кольского полуострова.

По просьбе Мурманской администрации по здравохранению был определен свинец в крови детей в возрасте 5-14 лет в трех областях: 2 группы (N=24 и 39) из Апатит, индустриального города; группа (N=47) из Ловозера, изолированной деревни саами; и последняя (N=14) из Краснощелья, удаленной деревни с саами, коми и ненецким населением. Неожиданно высокий уровень свинца в крови был найден в наиболее изолированной области, а именно в Краснощелье. Медиана концентрации свинца в Краснощелье была значительно выше ($p<0.01$ или $p<0.02$) значений из Ловозера и Апатит. В самой же группе из Краснощелья уровень свинца не зависил от пола. Процент детей со свинцом на уровне или выше уровня, требующего медицинского вмешательства, 0.48 мкмоль/л, был выше всего - 36% в Краснощелье, в то время как 4.2 и 9.8 % в двух группах из Апатит и 6 % в Ловозере. У всех, за исключением трех, из 124 исследованных детей концентрация ферритина была выше концентрации, указывающей на уменьшенные запасы железа (10 мкг/л для возраста < 14 лет) ; значения медианы концентрации ферритина сравнимы для всех четырех областей. Следовательно, отличием в содержании железа нельзя объяснить повышенную концентрацию свинца в крови в группе из Краснощелья. Вероятным объяснением может служить использование свинцовых пуль при охоте, являющейся традиционно важной для пропитания в этих местах.

Статья VI

Критическая оценка источников медицинских, статистических и профессиональных данных на Кольском полуострове.

Возможность изучения профессиональной экспозиции рабочих никелевой промышленности Кольского полуострова была подсказана первым отчетом 1992 года об возможном репродуктивном здоровье и развитии плода у женщин-рабочих никелевого комбината в России. Первоначальной целью исследования было узнать, могут ли быть использованы медицинские, статистические и профессиональные базы данных для получения информации об историях беременности, профессионального анамнеза и стиле жизни женщин. Проект было легко осуществить путем создания регистра всех рождений в трех городах с никелевыми комбинатами и проверкой правильности его содержания по медкартам из роддомов, гинекологических отделений больниц и районных поликлиник. Были также просмотрены записи муниципального регистрационного совета, регионального статистического совета по здоровью и записи(карты) с никелевого комбината. Исследование показало, что информация о репродуктивном здоровье и развитии плода и информация об историях рабочих мест являются приемлемыми. Расчеты размеров выборки показали, что групповое исследование будет легко выполнимо и удобно для определения повышенного риска спонтанных абортов с адекватной статистической значимостью и статистической силой. Такие исследования должны быть дополнены оценкой мониторинга окружающей среды, оценкой биологического мониторинга, позволяющего оценить в свою очередь экспозицию профессионально опасными веществами; и опросом рабочих для получения информации об их стиле жизни. Кольский регистр рождений, фиксирующий каждый отдельный случай, был рекомендован для изучения врожденных дефектов. Хорошо спланированное, полное эпидемиологическое исследование возможно благодаря наличию необходимых для анализа объектов; данных об репродуктивных исходах и об развитии плода, возможностью контролировать правильность получаемой информации и наличием удобных для дальнейшей работы профессиональных записей.

APPENDIX I: *Questionnaire*

REGISTRERINGSSKJEMA FOR PASIENTER TIL PROSJEKTET:
SAMANLIKNANDE STUDIER AV FØDEPASIENTER I NOREG OG RUSSLAND

MOR

1. **Alder** .... **Fødselsdato** ....

2. **Etnisk bakgrunn** ....

3. **Kor født** ....

4. **Når kom pasienten til stedet** ....

5. **Bosted over lengre perioder**- meir enn 6 mnd. ....
   - ....
   - ....

6. **Skolegang - antall år**..

7. **Yrke/arbeidsplass** ....

8. **Kor lenge borte frå jobb før fødsel?** (jfr. halveringstid for nikkel)...............................

9. **Tobakk** - antall sigaretter pr. dag..
   -røyking hos andre familiemedlemmer?..

10. **Alkohol** daglig ☐ ukentlig ☐ sjelden ☐ aldri ☐

11. **Faste medisiner?** nei ☐ ja ☐ **Hvis ja hvilke?**...
    ....

12. **Alvorlige sjukdomar** - generelt?..
    -i løpet av svangerskapet?..

13. **Et du eigendyrka mat?**
    I så fall kva? (fisk, kjøtt, grønnsaker, o.a.)..

14. **Inngår produkter frå lokalmiljøet i den daglege kosten?**
I så fall
kva?..

FØDSEL/BARN

Parietet .... **Lengde**...

Termin... **Hodeomkrets**..

Forløsningsdato................................. **Vekt på plasenta**......................................

Fødselsvekt på barn.......................... **APGAR**..

Gestasjonsalder ....uker **Prematur** ☐ **Dysmatur** ☐ **Postmatur** ☐

Misdannelser/
kommentarer:..

APPENDIX II: *Invitation and Consent Form*

INVITASJON TIL Å DELTA I ET FELLES
NORSK-RUSSISK FORSKNINGSPROSJEKT.

Kjære fødende kvinne.

Vi har i vårt land i lenger tid vært opptatt av mulige konsekvenser av forurensing av miljøet vi lever i. Du er herved invitert til å delta i en felles norsk-russisk undersøkelse om sammenheng mellom forurensing i omgivelsene og komplikasjoner under svangerskap og fødsel.

Fødeavdelingen vår deltar nå i en større internasjonal undersøkelse om disse forhold.Vi er mest interessert i de forhold som har tilknytning til den forurensing som kommer fra russisk side.Vi har solide data på hva denne forurensing har påført jord,luft og vann av skader,men vi har praktisk talt ingen data på hva dette kan medføre for mennesket under den mest følsomme perioden i livet,nemlig før vi blir født.

Vi har gjort en foreløpig undersøkelse i 1991 av tilsvarende forhold.Dette materialet er nå under analysering,og resultatene vil bli offentliggjort så snart de er ferdig.Denne type undersøkelser tar imidlertid lang tid,og i mellomtida er det av de respektive miljøvernministre i de arktiske land lagt opp til en større anlagt undersøkelse rundt Nord-Kalotten,der vi ønsker å delta.Det viktigste siktemålet er å kartlegge leveforhold i de arktiske strøk.Dersom vi finner skadelige forhold plikter vi å si fra om det,og dersom vi finner forhold som gjør det gunstig å bo i arktiske strøk må vi også si fra om det.

Det pågår nå et åpent og interessant medisinsk samarbeid mellom Norge og Russland,spesielt i sammenheng med forskning på miljørettet helsevern.
Vårt prosjekt er en del av et bredere samarbeid som nå er under utvikling.Vi tar tilsvarende prøver av fødekvinner på Kola og flere andre steder i Russland,likeledes gjøres dette flere steder i Norge.

Det vi ønsker er å ta en vanlig blodprøve av mor rett etter fødsel,som regel i sammenheng med rutineprøver som likevel skal tas.Vi ønsker en prøve fra morkaken som skal tas like etter at denne er kommet ut, likeledes urinprøve fra mor og barn så snart dette kan ordnes på naturlig måte.Disse prøvene blir frosset og senere analysert på blant annet tungmetaller,jern og fettstoffer etter vedtatte retningslinjer for den internasjonale undersøkelsen.

Denne informasjon blir gitt og vi ber om at bekreftelsen blir undertegnet før eller i forbindelse med innleggelsen før fødselen.

Hammerfest 1993

Jon Øyvind Odland	Kåre Augensen	Avdelingsjordmor
Prosjektleder,sign.	Avdelingsoverlege	

Bekreftelse på deltakelse i "Sammenlignende undersøkelser av fødepasienter i Norge og Russland":

Jeg ønsker å delta i den norsk-russiske undersøkelsen som er beskrevet.

Dato:

Underskrift:

PAPER I

Urinary nickel concentrations and selected pregnancy outcomes in delivering women and their newborns among arctic populations of Norway and Russia

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The two objectives of this study were to compare urinary nickel excretion in pregnant women and their newborns living in the Murmansk and Arkhangelsk Counties of Russia with that in comparable Norwegian populations living in Finnmark and the city of Bergen and to assess the influence on pregnancy outcome of different risk variables, specifically urinary nickel concentrations and questionnaire-based anamnestic information. Life-style information and urine samples were collected from 50 consecutive mother–infant pairs from hospital delivery departments in three Russian and three Norwegian communities. Pregnancy outcomes were verified from medical records. Urinary nickel excretion was significantly higher in the Russian communities, independent of the presence of a nickel refinery as a local environmental source. The birth weight and mean body mass index of the newborn children (BMIC) were significantly lower ($p < 0.001$) in the Russian groups, with or without adjustment for gestational age. A multivariate linear regression analysis indicated that maternal urinary nickel concentration had no impact on birth weight. The maternal body mass index (BMI) and maternal height were positive explanatory variables; maternal urinary creatinine is suggested as a weak negative factor. Smoking was shown to be a strong negative predictor only in the Norwegian group among whom there was a significantly higher smoking frequency ($p = 0.005$). The significant contribution of a country factor in the predictive model is interpreted to indicate that a number of important risk factors for low birth weight were not identified.

Introduction

Considerable attention is being paid to industrial pollution in the regions adjoining the Norwegian–Russian border, especially in relation to the substantial emissions of sulfur dioxide and metals by the nickel industry in the Kola Peninsula of Russia. Nearly half of the tonnage of metals released is nickel, with iron and copper other major contributors.[1] Extensive environmental damage has resulted from these pollutants and has generated considerable concern about public health in Russia, Norway and Finland. A Joint Norwegian–Russian Commission on Environmental Cooperation was established in 1988 and encouraged extensive investigation of the pollution of air, water, soil and biota.[2,3] By contrast, very little has been done on the investigation of human health, even though there has been considerable focus by the media on reproductive and developmental issues related to nickel exposure. Our interest in the present project derived from this public interest and had as its objective the determination of whether there is a scientific basis for this concern. We used a two-pronged approach: (i) an assessment of the exposure to nickel of pregnant women selected from the general public and its relation, together with other factors, to pregnancy outcome; (ii) an investigation of the reproductive health of female nickel workers. The results of the first component are reported in this study.

The reproductive/developmental effects of nickel have not been firmly established in humans, although some concern exists about apparent increases in spontaneous abortions and structural malformations (especially cardiovascular and musculoskeletal) in newborn babies whose mothers were employed in a Russian nickel refinery.[4,5] The evidence of teratogenic and developmental effects of nickel in animal studies is difficult to interpret with confidence.[6–8] Compared with cadmium,[9] lead[10] and mercury,[11] there is clearly a paucity of data concerning nickel exposure in relation to reproduction and pregnancy outcome. Further, the literature on nickel concentrations in body fluids during pregnancy is very scarce, and the suggested nickel urine reference values[12,13] or the results reported in surveys[14–16] do not include pregnant women or newborn children.

The present study had the following two specific objectives: (i) to compare urinary nickel excretion in pregnant women and their newborns living in the Murmansk and Arkhangelsk Counties of Russia with that in comparable Norwegian populations living in eastern Finnmark and the city of Bergen; (ii) to assess the influence on pregnancy outcome of different risk variables, specifically urinary nickel concentrations and questionnaire-based anamnestic information.

This study was approved by The Regional Ethical Committee, University of Tromsø, Norway, the Norwegian Data Inspectorate and the Regional Health Administrations of Murmansk and Arkhangelsk Counties.

Materials and methods

Study population and procedures

Personal contacts with colleagues in the different hospital delivery departments were established, and all procedures and protocols were provided in Norwegian, English and Russian.

The Russian geographic sites in our study were Nikel and Monchegorsk in Murmansk County and Arkhangelsk in Arkhangelsk County. Nikel (23 000 inhabitants) and Monchegorsk (65 000 inhabitants) are communities with nickel refining operations. Arkhangelsk is the biggest city on the White Sea, with almost 450 000 inhabitants and five big pulp and paper plants in the surrounding area, but no metal producing industry. The Norwegian reference cities were Kirkenes, Hammerfest and Bergen (Fig. 1). Kirkenes (approximately 4500 inhabitants) is located near the Russian–Norwegian border, 50 km from Nikel. The delivery department there receives women from the eastern part of Finnmark (total population, 28 000), the area geographically adjacent to the Russian border. Hammerfest (12 000 inhabitants) is a coastal city of Finnmark; the hospital delivery department there receives women from the western part of Finnmark (a total of 45 000 residents), including the main native Saami centres in Finnmark County. Bergen is the second biggest city of Norway in the southwest part of the country (total population, 220 000), with no major metal producing industry. It was included because it represents a non-Arctic urban community.

Information by questionnaire and urine samples were collected from at least 50 consecutive women presenting themselves to the hospital delivery departments in each location; the first-voided urine from their newborn babies was also obtained. The registration and sampling were performed in the following time periods: Arkhangelsk in April–May 1993; Kirkenes in November 1993–January 1994; Hammerfest in December 1993–January 1994; Bergen in June 1994; and Nikel and Monchegorsk in March–June 1994. Urines were collected from a total of 265 children: of these 137 were Russian (Nikel, $N=42$; Monchegorsk, $N=49$; and Arkhangelsk, $N=46$) and 128 were Norwegian (Kirkenes, $N=46$, Hammerfest, $N=51$; and Bergen, $N=31$). The women were asked to join the study by means of completing a consent form.

Very few cases interrupted the consecutive enrolment. Pregnant women in Kirkenes with prepartum complications or suspected delivery problems are sent to the Regional Hospital in Tromso. In the sampling period, two transfers were registered. Hammerfest hospital has a neonatal intensive care department and no cases were sent to Tromso before delivery during the sampling period. None of the delivering women refused to join the study. However, the complicated urine sampling procedure for neonates sometimes resulted in skin irritation, especially if the period before the first voiding was long. Consequently, neonatal urine samples could not be obtained from some of the infants: 4 cases in Arkhangelsk, 8 in Nikel, 1 in Monchegorsk, 19 in Bergen and 4 in Kirkenes. Even though anamnestic information and maternal samples were collected, the mother and child were excluded from the study's statistical analyses (see below).

Fig. 1 Schematic map of the Russian Barents region. Bergen is located in the southwest of Norway, and is not shown on the map. (Courtesy of Elin Hanssen, NILU, Tromso, Norway.)

In an interview, local midwives or gynaecologists administered a questionnaire that addressed the following particulars: age, parity, height and weight of mother, ethnic background, places of residence exceeding 6 months, schooling, occupation, smoking habits, alcohol consumption, medication, serious diseases and dietary habits related to local food intake. The following information was collected from the delivery department medical records about the mothers and births: maternal age, weight and height, Naegele term, date of birth, length and weight of baby, weight of placenta, Apgar score (clinical estimate of the conditions of an infant 1–5 min after birth), congenital malformations, gestational age and individual comments by the doctor or midwife. The informed consent form and collection of anamnestic information were completed before the delivery process started in order to minimize stress. Collection of the neonatal urine specimens was performed in a manner that avoided interruption of the delivery situation.

Sample collection and analysis

The urine of mothers was sampled at two stages: the first time at week 20 of pregnancy (only in Kirkenes and Nikel) and the second time together with blood sampling at 1–2 days postpartum. Maternal urine was collected directly into a disposable plastic cup for transfer to containers (NØD-0438 CERBO Norge A S, Oslo, Norway; volume, 20 mL); both the cup and the container were tested and found not to contaminate the urine samples with detectable amounts of nickel (<10 nmol L^{-1}). For sampling from the neonate immediately postpartum, a uridome (126-0004, Hollister Norge, Oslo, Norway) was attached by plasters to the child's genitalia until the first void was produced. For ethical reasons, we had to stop the sampling if the uridome irritated the very sensitive skin of the newborns. The urine samples were immediately frozen at -20 °C. Within 3 months, all the materials collected were transported frozen to the city of Bodo in Norway for storage in a -70 °C freezer.

After thawing, the urine samples were heated for 1 h at 95 °C in an oven to redissolve the urine precipitates and to ensure sterility. Urine was analysed without further pretreatment. Nickel in urine was measured by electrothermal atomic absorption spectrometry employing Zeeman-based Perkin-Elmer Model 5100 PC/HGA-600 and Perkin-Elmer SIMAA 6000/THGA graphite atomizer systems (Bodenseewerk Perkin-Elmer GmbH, Überlingen, Germany) calibrated with urine matched standard solutions.[17] The accuracy and precision of the measurements were assessed routinely by using human urine quality materials obtained from NycoMed Ltd., Oslo, Norway (Seronorm STE 101021 and 403125). The day-to-day variation of the nickel measurements in these reference materials was typically 10%. The average nickel concentrations of STE 101021 and 403125 human urine measured during the analysis period were 41 ± 5 nmol L^{-1} and 661 ± 56 nmol L^{-1} respectively. This is in good agreement with the manufacturer's recommended values of 43 and 681 nmol L^{-1}. The detection limit of the method used was 10 nmol L^{-1} of nickel. The creatinine content was measured by a Beckman Creatinine Analyser (Beckman Instruments, Brea, CA, USA) based on Jaffe's reaction.

Only in Nikel and Monchegorsk did the study group include women who worked in departments of the local refinery with potential exposure to nickel. It should be noted that, today, maternity leave starts 70 days before the anticipated date of delivery, while it was 56 days during the study period. Consequently, since urine samples in Monchegorsk were collected shortly after birth, the employees included were not recently occupationally exposed. In Nikel, a comparison is possible between samples collected while still at work (week 20) and postpartum.

Tap water samples (10 or 12) were collected in the following Russian communities: Nikel, Zapolyarniy, Monchegorsk, Arkhangelsk and Umba (the latter is located in the Kola Peninsula, south of Apatity on the White Sea). Homes were selected at random, the taps were flushed for a few minutes and the samples were collected directly into the same containers as used for the urine samples. The shipping, storage and analysis of the tap water were carried out in the same manner as for the urine specimens. In some cases, the water samples were not frozen and were analysed soon after their arrival at the laboratory in Oslo. Twenty-four hours before measurement, 0.5 mL 65% ultrapure nitric acid was added to each 20 mL sample in order to recover any surface-adsorbed nickel. Nickel measurements were performed in the same way as for urine, but calibration was against aqueous standard solutions. Surface water CSPS-SW1 (Spectrapure Standards Ltd., Oslo, Norway) trace-metal quality-control materials were used routinely. The day-to-day variation of the nickel measurements in these reference materials was typically 5%. The mean nickel concentration measured in CSPS-SW1, batch 102, was 164 ± 5 nmol L^{-1} (certified value 170 ± 9 nmol L^{-1} of nickel).

Statistical analysis

In the statistical assessment univariate analysis, analysis of variance and multiple linear regression analyses were employed. An association was accepted when the 95% confidence interval (CI) of the regression coefficient did not include zero. The Bartlett's test for homogeneity of variance and the Mantel–Haenszel and Fischer exact tests for comparison of proportions were used. In all groups, the urinary nickel results were highly skewed, and the non-parametric Wilcoxon rank sum test or the Kruskal–Wallis test for two groups were selected. Concentrations below the detection limit (DL) were arbitrarily assigned the value of 1 2DL. Information on the years of education, defined as years at school, was missing in the Russian questionnaire responses and could therefore not be included in the regression analysis. Neither could the answers about alcohol consumption be used, since 49 of the Russian respondents were reluctant to answer this section of the questionnaire. Since only one child was lighter than 2500 g among the Norwegian subjects, it was decided to use the birth weight outcome as a continuous variable instead of categorical (*i.e.* by defining low birth weight as <2500 g). Birth weights corresponding to gestational ages of 30–38 weeks were adjusted using the observed rate of increase of 166 g per week.

Results

Population characteristics

The mean age of the mothers was significantly higher in Norway than in Russia (27.7, range 17–40; 25.1, range 14–44; respectively; $p < 0.001$; Table 1). The percentage of the Norwegian mothers who were registered as smokers was 35.9%, of whom 13.3% might be regarded as heavy smokers (>10 cigarettes per day). By comparison, the Russian group had a smoking prevalence of 17.4%, none of them in the heavy smokers' category (Table 1). Complications related to pre-eclamptic conditions, specifically hypertension, oedema, proteinuria or anaemia, were significantly higher in the Russian group ($p = 0.03$). Local food consumption was categorized on the basis of whether the consumption of locally produced fish, meat, vegetables, mushrooms and berries occurred daily or not. The Monchegorsk group was not adequately examined in this component of the questionnaire to be considered in the interpretation of the data. The number of previous deliveries was significantly lower for the Russian subjects compared to the Norwegian group (means of 1.2 and 1.4 respectively; $p = 0.07$). Mean maternal weights at term were not different ($p = 0.11$), while mothers' mean height was significantly lower in the Russian group ($p < 0.001$). However, this did not result in different maternal body mass index (BMI) values ($p = 0.87$).

Pregnancy outcomes

Compared to the Norwegian results, the mean birth weight and body mass index of the newborn child (BMIC) were significantly lower in the Russian group ($p < 0.001$, Table 2), a difference that was retained after adjustment for gestational age or gender. Babies were somewhat longer in the Russian group ($p < 0.001$), while the differences in mean placenta weight and head circumference were not statistically significant. The children in Arkhangelsk had the lowest mean birth weight, with the highest values being reported in Kirkenes. The mean gestational age was significantly lower in Russia ($p < 0.001$), being the lowest in Arkhangelsk. These findings are consistent with a prevalence of 15% of children with birth weights of less than 2500 g in Arkhangelsk, compared to 3.5% in the two other Russian groups. Importantly, the difference between the mean birth weights for Russia and Norway remained significant ($p < 0.001$) when omitting the Arkhangelsk group in the comparison. As might be expected from the small number of subjects in our study,[18] only four children were born with registered malformations, two in Norway and two in Russia. One perinatal death (a child with hydrocephalus in Arkhangelsk) was identified.

In the Russian group, a total of 15 women were employed in the nickel industry, six in Nikel, who apparently worked in departments with little nickel exposure, and nine in Monchegorsk, who were potentially exposed in the electrorefining department. However, as already indicated, due to their maternity leave none of these women were recently occupationally exposed. The nine women working in the Monchegorsk electrorefinery had babies with an average birth weight of 3342 g (2540–4200), which is higher than the mean birth weight in the total Russian study population; one baby had a registered malformation (a minor limb defect). Seven of these nine nickel workers were daily smokers (77.8%), which exceeds the mean smoking frequency reported in Table 1; the delivery frequency was identical to that for the total Russian group (mean of 1.2).

Urinary nickel concentrations

The urinary nickel levels for the children and their mothers are provided in Table 3. Both the neonatal and maternal medians of the unadjusted urinary nickel concentrations were considerably higher among the Russian subjects compared to the Norwegians ($p < 0.001$). Values reported for the Norwegian group fall within the baseline reference interval of 9–100 nmol L^{-1};[12,13,19] while the Russian concentrations are mostly outside of it (maternal range at term, 5–2108 nmol L^{-1}). Creatinine adjustment did not affect these comparisons. Focusing on the towns of Nikel and Monchegorsk and the city of Arkhangelsk, we found that, for all three Russian centres, the median nickel concentrations were higher than for the Norwegian populations studied. Intercommunity comparisons for the three Russian populations revealed that, relative to Arkhangelsk, the median creatinine-adjusted nickel concentrations for Nikel and Monchegorsk were significantly higher ($p < 0.001$). This difference was not apparent for the unadjusted nickel concentrations. In the Nikel and Kirkenes groups, additional urines were also collected in the 20th week of pregnancy and at term. Neither the Nikel or the Kirkenes group demonstrated differences between the two stages of pregnancy ($p > 0.5$, $N = 42$ and $p > 0.5$, $N = 41$ respectively). Occupationally exposed women in Monchegorsk ($N = 9$, who had worked in the electrolysis tank house, but with no recent industrial exposure) had a median urinary nickel concentration

Table 1. Population characteristics

Characteristic	Russia ($N=137$)	Norway ($N=128$)	p Values
Mean maternal age[a]/years	25.1	27.7	<0.001[e]
(s, range)	(5.9, 14–44)	(5.3, 17–40)	
Mean number of deliveries[a]	1.2	1.4	0.07[e]
(range)	(0–4)	(0–5)	
Mean maternal weight[a]/kg	70.9	73.5	0.11[e]
(range)	(41–101)	(46–123)	
Mean maternal height[a]/cm	163	166	<0.001[e]
(range)	(150–174)	(155–182)	
Mean body mass index (BMI)/kg m^{-2}	26.7	26.6	0.87[e]
(range)	(17.3–39.6)	(18.4–38.0)	
Pre-eclamptic condition[ac]	26	12	0.03[f]
	(19.0%)	(9.4%)	
Smoking habits[b] (%)			
Non-smokers	82.6	64.1	0.005[f]
1–10 cigarettes per day	17.4	22.7	
>10 cigarettes per day	0	13.3	
Smoking frequency	17.4	35.9	
Local food intake (%)[bd]	86.1	61.0	<0.001[f]

[a]Based on medical records; for maternal height only, $N=121$ (Russia) and $N=93$ (Norway). [b]Based on questionnaire. [c]At least two of the parameters: hypertension, oedema, proteinuria. [d]Regular use of locally produced vegetables, potatoes, berries and/or locally produced fish or meat; the Monchegorsk group is not included (see text). [e]t-test. [f]Chi-squared test.

Table 2 Comparison between selected pregnancy outcomes in Russia and Norway

Outcome[a]	Russia ($N=137$)	Norway ($N=128$)	p Values
Mean birth weight/g	3195	3590	<0.001[b]
(s, range)	(579, 1400–5100)	(502, 2200–4960)	
Mean length of baby/cm	51.8	50.7	<0.001[b]
(range)	(41–58)	(45–58)	
BMIC/kg m^{-2}	11.9	13.9	<0.001[b]
(s, range)	(1.7, 7.5–18.2)	(1.4, 10.1–19.4)	
Mean placenta weight/g	582	621	0.06[b]
(range)	(300–900)	(350–1050)	
Mean gestational age/weeks	38.7	39.8	<0.001[b]
(range)	(31–42)	(36–42)	
Mean head circumference/cm	35.0	35.0	0.92[b]
(range)	(32–38)	(30–39)	

[a]All information is derived from medical records. [b]Comparison of country means by t-test.

Table 3 Median nickel urine concentrations of delivering women and their babies in Arctic areas of Russia and Norway (nmol L^{-1})[a]

	Group studied								
	Russia ($N=137$)	Nikel ($N=42$)	Monchegorsk ($N=49$)	Arkhangelsk ($N=46$)	Norway ($N=128$)	Kirkenes ($N=46$)	Hammerfest ($N=51$)	Bergen ($N=31$)	p Value[b]
Maternal urine nickel at term/nmol l^{-1}	85 5–2108	90 5–694	83 5–2108	85 19–1258	5 5–85	5 5–26	14 5–82	15 5–85	<0.001
Maternal urine nickel at term, adjusted for creatinine/nmol Ni per mmol creat	9 1–285	13 1–139	10 3–285	6 1–49	1 0.2–41	1 0.2–8	3 0.2–41	2 0.3–36	<0.001
Nickel in baby's first-voided urine/nmol L^{-1}	34 5–561	41 5–561	37 5–374	24 5–260	5 5–48	5 5–20	5 5–48	5 5–24	<0.001
Baby's urine nickel, adjusted for creatinine/nmol Ni per mmol creat	11 1–510	31 3–510	12 2–45	5 1–325	2 0.4–187	3 0.4–34	2 0.5–187	2 0.5–13	<0.001

[a]Median value and range are given. For statistical purposes, values below the DL of 10 nmol L^{-1} were set at ½DL. [b]For the comparison of the total Norwegian and Russian data sets, non-parametric statistics were used (see text).

of 66 nmol L^{-1}, somewhat less than that in the total Russian group (median value, 85 nmol L^{-1}).

Univariate linear regression

The results of the univariate analysis are provided in Table 4. The birth weight or the BMIC was selected as the dependent variable. The regression coefficient corresponding to the change in the baby's weight in grams per unit of the explanatory variable was first examined. For both the Russian and Norwegian subjects, maternal urinary creatinine is suggested as a weak negative predictor (not significant). For the total Russian group, there were no other variables significantly associated or even nearly so with the two outcomes. For the

Table 4 Linear regression analysis of birth weight

Variable	Russia Weight change (CI)[a]	Russia p Value[b]	Norway Weight change (CI)[a]	Norway p Value[b]	Russia/Norway (adjusted for country) Weight change (CI)[a]	Russia/Norway (adjusted for country) p Value[b]
Maternal Age (years)	8.5 (−8, 25)	>0.05	10 (−7, 27)	>0.05	9 (−3, 21)	>0.05
Smoking (categorical, amount smoked)[c]	116 (−86, 318)	>0.05	−193 (−312, −73)	<0.005	−91 (−200, 18)	>0.05
Local food consumption (categorical, yes/no)[c]	−82 (−366, 202)	>0.05	−181 (−359, −3)	<0.05	−146 (−302, 10)	>0.05
Pre-eclamptic conditions (categorical, yes/no)[c]	1.8 (−249, 252)	>0.05	−5 (−307, 297)	>0.05	0 (−190, 189)	>0.05
Number of deliveries	58 (−45, 161)	>0.05	23 (55, 101)	>0.05	38 (−25, 100)	>0.05
Gender of baby, M/F	64 (−136, 263)	>0.05	−126 (−316, 65)	>0.05	−19 (−158, 120)	>0.05
Maternal weight/kg	6 (−3, 15)	>0.05	12 (5, 19)	<0.001	9 (3–15)	<0.005
Maternal height/cm	−2 (−22, 18)	>0.05	21 (6, 36)	<0.005	10 (−3, 22)	>0.05
BMI/kg m^{-2}	16 (−7, 39)	>0.05	31 (11, 52)	<0.005	22 (6, 38)	<0.01
Maternal urine nickel/nmol L^{-1}	−0.1 (−0.5, 0.3)	>0.05	1 (−4, 6)	>0.05	−0.1 (−0.5, 0.3)	>0.05
Maternal urine creatinine/mmol L^{-1}	−8 (−23, 6)	>0.05	−13 (−32, 7)	>0.05	−10 (−21, 2)	>0.05
Child's urine nickel/nmol L^{-1}	−0.6 (−2.0, 0.8)	>0.05	−3 (−14, 8)	>0.05	−0.6 (−1.9, 0.7)	>0.05
Child's urine creatinine/mmol L^{-1}	12 (−15, 39)	>0.05	10 (−13, 33)	>0.05	11 (−6, 29)	>0.05
Maternal adjusted urine nickel/nmol Ni per mmol creat	−0.9 (−4, 2)	>0.05	9 (−8, 27)	>0.05	−3 (−6, 0.1)	>0.05
Child's adjusted urine nickel/nmol Ni per mmol creat	−0.6 (−2, 0.6)	>0.05	1 (−4, 6)	>0.05	−0.6 (−1.7, 0.6)	>0.05

[a]Weight change in grams per unit of explanatory variable; CI, 95% confidence interval. [b]Based on the partial F-statistic. [c]See Table 1 for classification.

combined Norwegian subjects, the following associations reached significance: maternal weight ($p<0.001$), maternal height ($p<0.005$), BMI ($p<0.005$), smoking ($p<0.005$) and local food consumption ($p<0.05$). On combining the Russian and Norwegian study groups and adjusting for country, the associations with maternal weight ($p<0.005$) and BMI ($p<0.01$) remained significant, as did the near significance of maternal urinary creatinine. Adjustment of birth weight for gestational age strengthened the maternal weight and BMI dependences (both $p<0.001$), but did not alter the remaining associations substantially.

For BMIC, there were no significant associations for the Russian subjects; among the Norwegian group, smoking was negatively correlated ($p<0.025$), while maternal weight ($p<0.025$) and BMI ($p<0.025$) were positively so. Only the maternal weight ($p<0.025$) and BMI ($p<0.01$) retained significance for the combined countries. As with birth weight, adjustment for gestational age strengthened the relationship with maternal weight and BMI (both $p<0.001$).

Log transformation or square transformation of the nickel concentrations added no additional information; neither did the grouping of birth weight by 500 g increments.

Multivariate linear regression

The variables for which significant or near-significant associations with birth weight were observed in either of the two countries (see Table 4) were tested in a multivariate model. Because a major focus of this study was a comparison of urinary nickel excretion, maternal urinary nickel was also carried forward. Maternal body weight was not included since it is related to BMI. By contrast, the exclusion of maternal height as an independent explanatory variable resulted in a significant loss of information. The model summarized in Table 5 shows BMI ($p<0.005$) and maternal height ($p<0.05$) as positive predictors, while the contribution of maternal urinary creatinine is negative (nearly significant); a very strong unspecified country factor is evident ($p<0.001$). The model was optimized[20] by removal of local food consumption and neonatal urinary creatinine. Judging by the partial *F*-statistic, the explanatory contributions of both of these variables were low and not statistically significant; that of maternal urinary nickel was zero. Introducing gestational age-adjusted birth weight as the dependent variable strengthened the positive predictive value of BMI ($p<0.001$) and maternal height ($p<0.025$) and weakened the country factor slightly ($p<0.01$), leaving the other predictors unchanged. In the corresponding multivariate model with BMIC as the dependent variable (Table 6), BMI ($p<0.01$ or 0.001) and the country factor ($p<0.001$) were the only notable variables (with or without adjustment for gestational age).

Table 5 Multivariate linear regression analysis model to predict birth weight for the combined Russian/Norwegian population[a,b]

Variable	Change in birth weight/g (95% CI)	p Value
Maternal urinary nickel/nmol L^{-1}	−1 (−6, 5)	>0.05
BMI/kg m^{-2}	25 (8, 42)	<0.005
Maternal height/cm	14 (0, 27)	<0.05
Maternal urinary creatinine/mmol L^{-1}	−10 (−22, 3)	>0.05
Smoking (0, 1–10 or >10 cigarettes)	−25 (−148, 99)	>0.05
Country (Russia/Norway)	315 (143, 487)	<0.001

[a]Since 52 maternal heights were not reported and the data sets for the other variables had some omissions, $N=200$ (see Table 1); all values are mutually adjusted. [b]The *F*-statistic for the model is 7.3, with d.f. 6 and 194; $p<0.001$.

Table 6 Multivariate linear regression analysis model to predict child's body mass index for the combined Russian/Norwegian population[a,b]

Variable	Change in birth weight/g (95% CI)	p Value
Maternal urinary nickel/nmol L^{-1}	0 (−0.03, 0.004)	>0.05
BMI/kg m^{-2}	0.07 (0.02, 0.12)	<0.01
Maternal height/cm	0.01 (−0.03, 0.05)	>0.05
Maternal urinary creatinine/mmol L^{-1}	0.002 (−0.03, 0.04)	>0.05
Smoking (0, 1–10 or >10 cigarettes per day)	−0.06 (−0.42, 0.31)	>0.05
Country (Russia/Norway)	1.9 (1.4, 2.4)	<0.001

[a]Since 52 maternal heights were not reported and the data sets for the other variables had some omissions, $N=199$ (see Table 1); all values are mutually adjusted. [b]The F-statistic for the model is 15.8, with d.f. 6 and 193; $p<0.001$.

Birth weight in relation to neonatal urinary nickel concentrations

Group analysis of neonatal urinary nickel concentrations (group 1, <15 nmol L^{-1}; group 2, 15–170 nmol L^{-1}; group 3, >170 nmol L^{-1}) demonstrated no evidence for a dependence of birth weight (or BMIC; data not reported) on neonatal urinary nickel concentrations (Norwegian group, $p=0.5$; Russian group, $p=0.3$ or 0.2; all relative to group 1 by t-test). Neither was a risk for reduced birth weight apparent when the weights were compared for urinary nickel levels below and above 34 nmol L^{-1}, corresponding to the mean reference background concentration reported for non-pregnant adults.[19]

Nickel in tap water

Russian communities with local nickel refineries, namely Nikel and Zapolyarniy (see Fig. 1), had significantly higher nickel levels in the drinking water (median values of 1224 and 578 nmol L^{-1}, respectively) compared to the four other Russian and two Norwegian locations (medians in the range 9–85 nmol l^{-1}, $p<0.001$). In the Russian communities with no local point sources of nickel, specifically Kirovsk, Apatity and Umba, values were closer to the Norwegian levels (median values of 9, 85 and 14 nmol L^{-1} respectively). Ten out of 12 tap water samples from Arkhangelsk were at the DL or below (all from private kitchens): the two detectable values were 12 and 20 nmol L^{-1} (collected at the Institute of Physiology, Ural Branch of Russian Academy of Science, Arkhangelsk, and a private kitchen of a colleague).

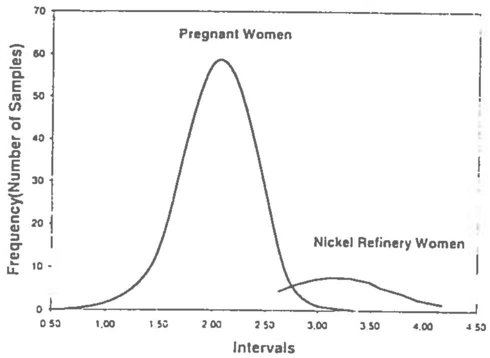

Fig. 2 A comparison of the frequency distribution of the log-transformed urinary nickel data for the Russian groups surveyed in the present study ($N=179$; includes the results from week 20 of pregnancy in Nikel) with that ($N=52$) reported for female workers employed in the Electrorefinery Department of the Severonickel operation in Monchegorsk.[8] The sample collection and analytical procedures were identical to those described in the text; urine samples were collected in May 1996 and correspond to the first morning void collected at home to minimize inadvertent contamination. The median and range of the nickel concentrations for the nickel workers were 1496 (289–14620) nmol L^{-1}, compared to 99 (5–2108) nmol L^{-1} in the total Russian population in the current study. Ambient air nickel levels in the Monchegorsk Electrorefinery Department[8] were in the range 60–1200 μg m^{-3}, which appear to be higher by about a factor of 1000 to 10000 or more than reported air levels for the town of Nikel and the surrounding area, including the Norwegian–Russian border area.[14,15]

Discussion

Urinary nickel concentrations

The comparison of the urinary nickel concentrations reported in the present study with published background reference intervals[12,13,19] (<100 nmol L^{-1}) is beneficial. Clearly, the results for the Russian study groups exceed this reference upper limit, while the values for the Norwegian communities are well below it. The slightly higher creatinine-adjusted concentrations observed for the Nikel and Monchegorsk populations relative to Arkhangelsk ($p<0.001$) suggest some environmental contribution due to the presence of the local nickel smelters. Such an impact of nickel refining on non-occupationally exposed community members has been reported previously for the city of Sudbury, Ontario.[21,22] It is interesting to compare the Russian data for the pregnant women surveyed with recently obtained results for Russian females working in a Kola Peninsula nickel electrorefinery. This is done in Fig. 2. It is evident from this figure that the two groups compared have separate frequency distribution patterns. The overlap between them is minimal.

There has been some suggestion that nickel excretion is increased during pregnancy, parturition and postpartum.[23] Earlier reports of drastic increases in serum or urinary nickel during parturition and postpartum suffered from severe analytical deficiencies and therefore can only be interpreted with considerable caution.[6] Birth-associated trauma may have contributed to the slightly higher urinary nickel concentrations in the present pregnant females, when compared to other adults. Making comparisons for Nikel, the median urinary nickel value for the pregnant women of the present study was 90 nmol L^{-1}, compared to 58 nmol L^{-1} for other residents ($N=371$, 70% female).[15]

The higher urinary nickel excretion among the Russian groups does not have an obvious explanation. Nickel in tap water, perhaps in combination with enhanced air levels, probably accounts for the higher creatinine-adjusted urinary nickel levels observed for Nikel and Monchegorsk, compared to Arkhangelsk. Since there are no nickel refineries or any other obvious nickel point source in Arkhangelsk, other explanations are required to account for the major portion of the Russian/Norwegian urinary nickel anomaly. It is known that certain foodstuffs are relatively enriched in nickel, such as cocoa, nuts, dried legumes and certain grains.[7,24] Special dietary sources in the Russian community might therefore be suspect. Leaching into drinking water from nickel-plated pipes or from cooking utensils constitutes another explanation. Oral prostheses are in use in Russia that apparently have significant nickel contents, and this may well be an unexpected source of nickel.[8]

To our knowledge, nickel in first-voided urines of neonates has not been reported previously. Because so many urinary nickel concentrations in both Norwegian mothers and neonates were below or at the DL, it is difficult to compare their relative magnitudes. This is not the case for the Russian population studied. A comparison of maternal and neonatal creatinine-adjusted nickel levels shows the latter to be lower ($p<0.001$). From the perspective of the glomerular filtration rate (GFR), this is not unexpected. At birth, the neonatal GFR appears to be about 20% of adult values.[25]

Birth weight as a pregnancy outcome

Birth weight is recognized as an important indicator of the health status of neonates.[26] Temporal changes in this parameter may serve as an index to socioeconomic conditions that impact on reproductive and developmental health. It is also known to be sensitive to adverse environmental conditions, as illustrated by cigarette smoking. As a pregnancy outcome, birth weight permits an outcome comparison unaffected by cultural differences and medical uncertainties such as outcome definitions. Congenital malformations and perinatal morbidity are examples. However, birth weight has some disadvantages as a dependent variable for pregnancy outcome, due to genetic differences.[27,28] On the other hand, the BMIC has been suggested to have some advantages as an index to the nutritional status of newborn children.[29–31] It would appear that the BMIC is somewhat less sensitive to the explanatory variables examined in our study.

Among the statistically significant associations reported in Table 4 for the linear regression between birth weight and a number of explanatory variables are those recognized for having a known positive impact on birth weight (*i.e.* maternal weight, maternal height, BMI, number of deliveries)[32] or a negative effect (*i.e.* smoking, hypertensive pregnancy complications).[32–34] BMI is considered a measure of body fatness. It is strongly influenced by age and sex, but not by ethnicity.[35] Since we are dealing with females of comparable age, BMI may thus be taken as a suitable index of adipose tissue mass. Although not included in the analysis, alcohol consumption during pregnancy is also well known to reduce birth weight. It is of interest that the 35.9% smoking frequency found among the Norwegian group concurs almost exactly with the proportion of subjects identified as daily smokers prior to pregnancy in a recent survey of 4766 pregnant Norwegian women.[36]

It is tempting to interpret the apparent but weak negative impact of maternal urinary creatinine as indicative of subclinical pre-eclamptic manifestations. In support, it is noted that pre-eclampsia was found to be more prevalent in the Russian communities ($p=0.03$). Interestingly, past pre-eclampsia appears to increase the risk of microalbuminuria,[37] and increased urinary creatinine levels have been noted as early as week 19 of gestation in patients who subsequently developed pregnancy-induced hypertension.[38] The positive association suggested for neonatal urinary creatinine and birth weight (not significant) also seems inherently reasonable. One might expect, by analogy to adults, that body mass or surface area determines the rate of urinary creatinine excretion. The latter has indeed been correlated with birth weight.[39] Local food intake may constitute a nutritional factor or environmental contaminant issue. However, caution must be practised in interpreting at face value the associations suggested by single regressions, even when statistically significant, because of inter-predictor influences and possible correlations among variables. Consequently, the outcome of a multiple regression analysis of the explanatory variables should be consulted before acceptance of the suggested associations.

The univariate linear regression data and the multivariate model reinforce that smoking is a predictor of low birth weight. The data presented suggest it reaches significance only if the smoking rate is moderately high, such as seen among the Norwegian subjects. The retention of BMI ($p<0.005$) and maternal height ($p<0.05$) in the multivariate model conforms with the general acceptance of maternal weight and height as positive determinants. Similarly, urinary creatinine as a near significant variable in the linear and multiple regressions suggests that this parameter might be more sensitive in explaining birth weight than clinical diagnosis of the pre-eclamptic condition as a categorical variable. It is obvious from the magnitude of the 'country' slope factor in Table 5 that we have failed to identify important predictors of birth weight. The replacement of birth weight by BMIC did not improve the model, although adjusting for gestational age strengthened the BMI influence and left the unspecified country factor unchanged. Presumably, these results reflect unidentified differences in economic conditions, cultural practices or nutritional factors.

Limitations of the study

A number of information biases can be identified. Answers concerning the consumption of local food were not provided in the Russian community of Monchegorsk. The reason for this may reflect the decision by the local interviewer not to emphasize this component. The refusal by 36% of the Russian respondents to provide information about alcohol consumption suggests that this topic is culturally sensitive. Even fewer individuals responded to educational background questions there. Inconsistency between interviewers is also of concern. However, this was unavoidable since so many different communities were involved. Further, the questionnaire was translated from Norwegian into Russian and this may have had a steering effect on some of the questions. Of course, inherent ambiguities in the questions may have influenced the consistency of the answers. In our estimation, the discrepancies between Norwegian and Russian physicians in classifying pregnancy complications and outcomes were minimal. An example is the diagnosis of the pre-eclamptic condition.

Selection bias might have occurred for two reasons, namely transfer of cases with complications to regional hospitals and the exclusion from the statistical treatment of mothers and their neonates because of the unavailability of neonatal urine samples. Patient transfers were few and were registered. Inclusion of the neonatal weights for those without urinary nickel samples only reduces the difference between the Russian and Norwegian birth weight means by 4 g, which does not affect the significance test ($p<0.001$). Clearly, the significant Russian/Norwegian dissimilarity in birth weights is not explained by gestational age differences.

Although many explanatory variables were examined, it is likely that others exist, as well as unidentified confounders. However, there is evidence that this may not be too critical. In two overview reports on our work, one on essential trace elements (copper, zinc, iron and selenium)[40] and the other on metal pollutants (cadmium, lead and mercury)[1] in the peripheral blood compartment of many of the individuals in the present study, no obvious concentration differences that might be expected to influence birth weight appeared to exist between the Norwegian and Russian groups. For example, the iron status of pregnant women was somewhat better in Russia than in Norway, and serum zinc levels were low in both countries relative to established reference intervals.[40] Whole blood cadmium and mercury concentrations were higher in the Norwegian communities than in Russia, while it was the reverse order for lead. The mean Russian lead level of 0.18 μmol L^{-1} in whole blood was within the international background reference interval of <0.20 μmol L^{-1}.

Due to logistical and technical limitations, as well as economic restrictions, the sample size for each country was too small to detect differences in the incidence of congenital defects. Much larger populations need to be examined to identify such outcomes with adequate statistical power, as they are relatively rare.[18] The small number of cases identified in the present study is consistent with this.

Although we made every effort to minimize inadvertent contamination of the samples, the lack of opportunity to be personally involved in the early stages of the sample history (*i.e.* collection, handling, storage and transport to the laboratory) limited our ability to control the contamination risk. This may account for some of the outliers corresponding to the highest urinary nickel concentrations.

Concluding remarks

It is interesting that two physical parameters (BMI and height), a metabolic measure (maternal urinary creatinine excretion) and a life-style factor (smoking) were the strongest predictors of neonatal birth weight in this combined Russian/Norwegian study population. The unimportance of urinary nickel excretion, and thus nickel exposure, as an explanatory variable for birth weight is consistent with the recent conclusion of the Norwegian–Russian Health Study that no major health effects can be assigned to nickel as an air pollutant in the vicinity of the nickel refining operations in Nikel and Zapolyarniy.[16] This is not surprising. The local ambient air nickel concentrations there are low, although above background (54 ng m^{-3} compared to 23 ng m^{-3} respectively; measured as the respirable fraction, which seems to be comparable to the inhalable fraction in this instance[15,16]). It may be concluded from the Nikel and Monchegorsk urinary nickel data that the nickel refineries as local point sources only minimally affect the body burden of nickel.

The above conclusion should not be extended to females occupationally exposed to nickel for the following reasons. First, nickel is known to be transferred readily across the placenta.[41,42] Since nickel in urine is proportional to nickel in the blood plasma compartment,[22] it may be inferred that serum nickel also constitutes an index to embryonic or foetal exposure. Because of the high occupational nickel exposures experienced by these workers (see Fig. 2[8,43,44]), *in utero* exposure cannot be dismissed. Second, concern has been expressed about increases in spontaneous abortions among females who work in the nickel electrorefinery at Monchegorsk.[5] An apparent increase in selected congenital malformations was also noted. Third, mechanistically speaking,[26] nickel compounds are potentially teratogenic and embryotoxic because they are genotoxic. Respiratory tract cancers have been associated with occupational exposures to water-soluble and particulate (mostly oxides and sulfides) forms.[43,45,46] Clearly, follow-up studies are needed. We have recently illustrated that a comprehensive epidemiological assessment of reproductive and developmental health among female nickel refinery workers in the Kola Peninsula is technically feasible.[8]

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PAPER II

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ORIGINAL ARTICLE

Concentrations of essential trace elements in maternal serum and the effect on birth weight and newborn body mass index in sub-arctic and arctic populations of Norway and Russia

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Background. This project is part of an assessment of the impact of environmental factors on human health in the Kola Peninsula of Russia and the neighboring arctic area of Norway. Pregnant women and their newborns were studied to explore a relationship between maternal status of essential metals and birth weight.
Methods. Life-style information and serum specimens were collected from at least 50 consecutive mother-infant pairs from hospital delivery departments in three Russian and three Norwegian communities (N=151 and 167, respectively). Pregnancy outcomes were verified by consulting medical records. Copper, selenium and zinc in serum were determined by atomic absorption spectrometry and ferritin by an automated analyzer method.
Results. Mean birth weight and child's body mass index (BMIC) were significantly lower in the Russian group (p<0.001), with or without adjustment for gestational age. Copper, iron (as ferritin) and selenium serum concentrations were in the normal range, while zinc levels in both countries were mostly below the lower limit (10.8 µmol/L) of reported reference intervals. A positive correlation between zinc and birth weight or BMIC was only observed for concentrations exceeding 10.8 µmol/L. Analysis by quartiles showed that maternal urinary creatinine and birth weight were negatively correlated (p=0.001). The influence of the different elements on BMIC, grouped by quartiles, was significantly positive only for selenium (p=0.03) and ferritin (p=0.02), while there was no significant relationship for copper or zinc. Adjustment of birth weight and BMIC for gestational age did not alter substantially the various associations indicated.
Conclusions. With the exception of zinc, the mineral status of delivering women in arctic and sub-arctic regions of Norway and western Russia appears to be adequate. The significantly lower BMIC for the Russian group suggests the likely occurrence of nutritional deficiencies during pregnancy in Russia. However, the significant contribution of a country factor in the predictive model implies that the maternal serum trace-element concentrations explored in this study are incomplete indicators of fetal undernourishment.

Key words: arctic; essential elements; pregnancy outcome

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A number of publications have recently explored the effect of environmental pollution on human health in subarctic and arctic areas of Norway and Russia (1–5). In a recent paper (6), we compared

Abbreviations:
AMAP: Arctic Monitoring and Assessment Programme; ANOVA: analysis of variance; BMI: body mass index; BMIC: body mass index of child.

the urinary nickel excretion in pregnant women and their newborns living in Murmansk and Arkhangelsk Counties of Russia with Norwegian populations living in Finnmark and the city of Bergen. A significant contribution of a country factor in the multivariate analysis indicated that other risk factors for low birth weight should be identified. The status of trace elements has been thoroughly discussed both in normal populations and in connection to pregnancy outcome in Nordic communities (7, 8), but no assessments have been performed in arctic populations. To elucidate this aspect, maternal serum concentrations of four important elements essential to fetal development were measured, namely copper, iron (as ferritin), selenium and zinc. A preliminary and incomplete report of the observed concentrations of these four elements has appeared elsewhere (9). The aim of the study described was two-fold:

(1) To compare concentrations of different essential elements in sera of delivering women living in the north-western part of Russia with those in populations living in northern Norway and the city of Bergen in the south-west of Norway:
(2) To assess the influence on birth weight and BMIC of the maternal copper, iron, selenium and zinc status and questionnaire-based anamnestic information.

This study was approved by The Regional Ethical Committee, University of Tromsø, Norway: the Norwegian Data Inspectorate and the Regional Health Administrations of Murmansk and Arkhangelsk Counties.

Material

Personal contacts with colleagues in the different hospital delivery departments were established, and all procedures and protocols were provided in Norwegian, English and Russian. The Russian geographic sites in our study were Nikel, Monchegorsk and Arkhangelsk (Fig. 1). Nikel (23 000 inhabitants) is a community close to the Russian-Norwegian border with a population mostly employed in primary nickel refining operations. Monchegorsk (65 000 inhabitants) is the biggest nickel refining center in the Kola Peninsula. Arkhangelsk is the largest city on the White Sea, with 419 000 inhabitants and five pulp and paper plants of substantial size in the surrounding area, but no metal producing industry. It is located south of the Arctic Circle, at 64° latitude. The Norwegian cities were Kirkenes, Hammerfest and Bergen (Fig. 1). Kirkenes (approximately 4500 inhabitants) is located near the Russian-Norwegian border, 50 km from Nikel. The Kirkenes delivery department receives women from the eastern part of Finnmark (total population 28 000), the area geographically adjacent to the Russian border. Hammerfest (12 000 inhabitants) is a coastal city of Finnmark; the hospital delivery department there receives women from the western part of Finnmark (a total of 45 000 residents), including the main native Saami centers in Finnmark County. Bergen (60° latitude) is the second biggest city of Norway in the south-west part of the country (total population 220 000), with no heavy industry. It was included because it represents a non-arctic, urban community.

Information by questionnaire, serum, urine and placenta specimens were collected from at least 50 consecutive patients presenting themselves to the hospital delivery departments in each location. The enrolment and sampling were performed in the following time periods: Arkhangelsk April – May 1993; Kirkenes, Hammerfest, Bergen, Nikel and Monchegorsk November 1993 – June 1994. Body fluid specimens were collected from a total of 318 new mothers; of these 151 were Russian (Nikel, Monchegorsk and Arkhangelsk) and 167 were Norwegian (Kirkenes, Hammerfest and Bergen). The women were asked to join the study by completing a consent form. Medical records in hospital delivery departments were consulted as appropriate.

Pregnant women in Kirkenes with prepartum complications or suspected delivery problems are sent to the Regional Hospital in Tromsø. In the sampling period, a total of two such transfers were registered. Hammerfest hospital has a neonatal intensive care department and no cases were sent to Tromsø before delivery during the sampling period. None of the pregnant expectant mothers refused to join the study.

Methods

In an interview, local midwives or gynecologists administered a questionnaire to the expectant mothers to secure the following personal details: age, parity, height and weight of mother, ethnic background, places of residence exceeding six months, schooling, occupation, smoking habits, alcohol consumption, medication, serious diseases before or during pregnancy and dietary habits related to local food intake. The dietary question in the interview was meant as a very simple indicator of the amount of daily intake of locally produced food, like meat, fish, potatoes, berries, and mushrooms, and did not constitute a detailed food frequency assessment. Delivery department derived

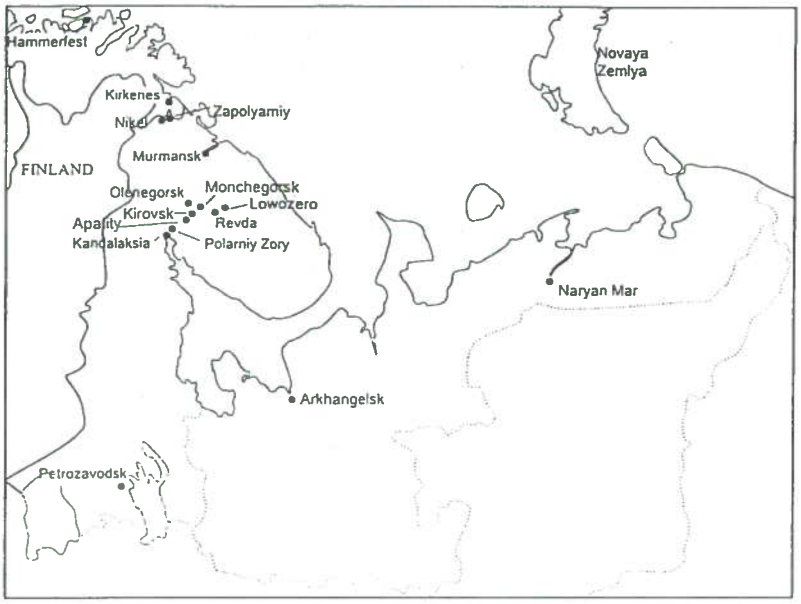

Fig. 1. Schematic map of the Russian Barents region. Bergen is located in the south-west of Norway, and is not shown on the map. Courtesy of Elin Hanssen, NILU, Tromso, Norway.

information included Naegele term, date of delivery, length and weight of baby, weight of placenta, APGAR score, congenital malformations, gestational age, and individual comments by the doctor or midwife. Enrolment, completion of the informed consent form and the questionnaire, and specimen collection were done before the delivery process started in order to minimize stress. Years of education, defined as years at school, as well as alcohol consumption details were missing in the questionnaire responses by the Russian participants and could not therefore be included in the multivariate analyses.

Specimens of antecubital vein blood from the mother (immediately postpartum) were taken in tubes (Sarstedt 02.264.020 10 ml Monovette, AH 23510) after installing a Viggo Spectramed venflon (1.4 mm, 17 Gauge L 45 mm) in the vena cubiti. Maternal serum was separated by centrifugation and transferred to tubes (Sarstedt 127–4004) for storage at −20°C. After each field trip, samples were immediately transported frozen to Norway, and kept at −20°C until analysis. Maternal urine specimens were stored and transported in an identical manner. Collection details were provided previously (6). The sampling equipment was tested for possible elemental contamination by leaching with 0.5% nitric acid and the concentrations found were below the detection limits of the methods. Copper and zinc were determined by flame atomic absorption spectrometry without dilution of the serum samples, applying the microcup technique. Calibration curves were constructed using matrix-matched standards prepared from Seronorm animal serum (Sero Ltd, Billingstad, Norway). The accuracy and reproducibility of the method were ensured using Seronorm human serum reference material (Nycomed, Norway). The concentrations found for both metals agreed well (±4%) with the values recommended by the manufacturer; typical within-day and between days variations of the quality control materials were 2 and 4%, respectively. Selenium in serum was measured by electrothermal atomic absorption spectrometry (10). Figures of merit for the measurement of selenium using Seronorm human serum quality control materials were within ±5% of the certified values; within- and between- days variations were 2 and 4%, respectively. The detection limits of the methods (3×s.d.) were 0.08 (Cu), 0.1 (Zn) and 0.04 (Se) µmol/L. The clinical chemical parameters, including iron and ferritin, were measured by a Hitachi 917 autoanalyzer using standard kits from Boehringer-Mannheim. The creatinine content was

Table I. Population characteristics, Russia and Norway

Characteristic	Russia (N=151)[1]	Norway (N=167)[2]	p-values
Mean maternal age, years[3]	25.1	28.0	<0.001[8]
(s.d.)	(5.8)	(5.1)	
Mean number of deliveries[3]	1.2	1.4	0.04[8]
Mean body mass index (BMI; kg/m²)[3]	26.8[7]	27.1[7]	0.7[8]
Pre-eclamptic complications of pregnancy[3,4]	21.2	7.2	<0.001[9]
Smoking habits (%):[5]			
Non-smokers	76.8	63.8	<0.001[9]
1–10 cigarettes/day	20.5	22.7	
>10 cigarettes/day	2.6	13.5	
Local food intake[5,6] (%):	83.4	53.3	<0.001[9]

[1] Number of individuals: Arkhangelsk, 51; Nikel, 50; Monchegorsk, 50.
[2] Number of individuals: Kirkenes, 51; Hammerfest, 56; Bergen, 60.
[3] Based on medical records.
[4] Pre-eclamptic conditions: hypertension, edema and/or proteinuria.
[5] Based on questionnaire.
[6] Regular use of locally produced vegetables, potatoes, berries and/or locally produced fish or meat.
[7] Number of individuals: Russia, 133; Norway, 124.
[8] T-test.
[9] Chi-squared test.

measured by a Beckman Creatinine Analyser based on Jaffe's reaction (6). In all cases, standard analytical protocols were employed.

For the statistical assessment, birth weight and children's body mass index (BMIC) were chosen as the outcome variables. For univariate analysis, multiple linear regression and ANOVA, the Epi Info 6, Version 6.04a, July 1996 (World Health Organization, Geneva, Switzerland) and the SAS statistical software packages were employed. An association was accepted when the 95% confidence interval (CI) of the regression coefficient did not include zero. The Bartlett's test for homogeneity of variance and the Mantel-Haenszel and Fischer exact tests for comparison of proportions were used. Since only two children were lighter than 2500 g in the Norwegian group, it was decided to use the birth weight outcome as a continuous variable instead of categorical (i.e., by defining low birth weight as <2500 g). Birth weights corresponding to gestational ages of 30–38 weeks were adjusted using the observed rate of increase of 166 g/week.

Results

Population characteristics

A number of population characteristics are compared in Table I. Maternal age, number of deliveries, and smoking habits in the Norwegian group were significantly higher (p<0.001, p=0.04, and p<0.001, respectively). The Russian participants had a higher prevalence of pre-eclamptic complications and greater frequency of local food intake (p<0.001 in both cases). There was no significant difference in maternal body mass index at term (BMI, p=0.7).

Pregnancy outcomes

The mean birth weight was significantly higher in the Norwegian group: 3584 (2150–4960) g compared to 3185 (1400–5100) g in Russia, p<0.001 (Table II), with or without adjustment for gestational age or gender. By contrast, newborn babies were longer in the Russian study groups (p= 0.002). This is reflected in BMIC, which was lower in the Russian neonates (p<0.001).

The mean gestational age was lower in Russia; 38.7 versus 39.8 weeks (p<0.001). Although placental weight was higher in Norway, the difference did not reach significance (p=0.3). The number of neonatal malformations reported in both countries were too small for a meaningful comparison: two children in the Russian study group had a registered congenital malformation (one hydrocephalus in Arkhangelsk, one minor heart defect in Monchegorsk), while the five registered malformations reported for Norway included two limb defects and

Table II. Comparison between selected pregnancy outcomes in Russian and Norwegian populations

Pregnancy Outcome[1]	Russian population N=151	Norwegian population N=167	p-values[2]
Mean birth weight, g	3185	3584	<0.001
(s.d.)	(612)	(509)	
Range	1400–5100	2150–4960	
Mean length of baby, cm	51.6	50.6	0.002
(s.d.)	(3.4)	(2.1)	
Mean body mass index of children, kg/m² (s.d.)	11.9 (1.7)	13.9 (1.3)	<0.001
Mean placenta weight, g	585[4]	607[5]	0.3
(s.d.)	(141)	(158)	
Mean gestational age, weeks	38.7	39.8[5]	<0.001
(s.d.)	(1.9)	(1.3)	
Neonatal malformations[3] (%)	1.3	3.0	

[1] All information is derived from medical records; 1 perinatal death (the child with hydrocephalus in Arkhangelsk), but no still births in the period of data collection.
[2] T-test, unless indicated otherwise.
[3] Malformations: Russian group: 2 (1 hydrocephalus in Arkhangelsk, 1 minor heart defect in Monchegorsk). Norwegian group: 5 (2 limb defects, 3 minor heart malformations).
[4] Number of individuals (N) 101.
[5] N=153.

Table III. Mean concentrations (s.d.) and range of essential elements in serum (S) of delivering women in Arctic Areas of Russia and Norway with accepted references intervals

Element	Russia	Norway	*p*-value[1]	Accepted intervals (11, 12, 13, 14)
Copper (S), µmol/L	35.1 (6.5) 18.5–57.0 *N*=110	37.3 (8.2) 16.2–68.6 *N*=150	0.02	18.5–47.4 (end of term)
Zinc (S), µmol/L	8.2 (1.7) 4.9–14.4 *N*=107	8.5 (3.2) 3.2–16.5 *N*=150	0.3	10.8–22.9
Selenium (S), µmol/L	1.0 (0.2) 0.6–1.6 *N*=108	1.1 (0.2) 0.5–2.0 *N*=149	0.2	0.7–1.6
Ferritin (S), µl/L	23.5 (33.8) 3–245 *N*=150	24.5 (19.6) 5–157 *N*=153	0.8	7–133

[1] *T*-test.

three minor heart malformations. One perinatal death was reported in the sampling periods.

Serum concentrations of essential elements

Mean concentrations of the four essential elements determined in maternal sera are presented in Table III. The data for all the measured elements in our study were normally distributed. The copper values for both countries were mostly within the accepted concentration interval, although the mean was somewhat higher in Norway ($p=0.02$). Serum zinc levels were generally below reported reference levels, even taking into account the known physiological decrease in concentrations during pregnancy (13). Splitting the Norwegian group by community, the southern Norwegian group of Bergen had 32% of the values below the generally accepted lower limit (10.8 µmol/L), while in the arctic Norwegian group 100% were below this value; in Russia 93.5% of the zinc concentrations were below 10.8 µmol/L. There was no significant difference between the countries ($p=0.3$). The selenium levels conformed to the accepted reference interval in both Norway and Russia, showing no significant difference. By contrast, ferritin concentrations showed a wide range in both countries; but the means were indistinguishable ($p=0.8$).

Univariate linear regression

The outcome of univariate linear regression analyses of the four different essential elements and questionnaire variables are shown in Table IV, with birth weight as the dependent variable. Both national and country-adjusted data are provided. The regression coefficient corresponds to the change in birthweight in grams per unit of the examined explanatory variable. None of the essential elements in serum were significant predictors of birth weight. However, by grouping the zinc concentrations, we find the zinc to be positively correlated with unadjusted birth weight only for the group ($N=41$) with concentrations >10.8 µmol/L ($p<0.025$). Even for the small group of individuals ($N=25$) with very low zinc values, <5.5 µmol/L, no negative correlation was evident. Of the other variables, maternal urinary creatinine is a weak negative predictor ($p>0.05$, with a β-coefficient of −9.3 [CI −20.7–2.0]). Maternal age, number of deliveries, BMI, and maternal weight were significant positive predictors ($0.05<p>0.001$), while maternal smoking suppressed birth weight ($p<0.025$). The influence of the country factor is highly significant ($p<0.001$).

Adjustment of birth weight for gestational age had no substantial impact on the linear associations summarized in Table IV.

Table IV. Univariate linear regression analysis of birth weight. Weight change in g/Unit (95% CI) and *p*-value. Crude and adjusted for country

Variable	Russia	*p*	Norway	*p*	Total group, adjusted for country	*p*
Maternal copper (S, µmol/L)	−0.5 (−18.7–17.8)	>0.05	5.7 (−4.1–15.5)	>0.05	3.8 (−5.3–12.8)	>0.05
Maternal zinc (S, µmol/L)	−19.8 (−90.7–51.2)	>0.05	−5.8 (−31.5–19.9)	>0.05	−8.2 (−34.2–17.7)	>0.05
Maternal selenium (S, µmol/L)	335.4 (−273.4–944.3)	>0.05	59.0 (−359.1–477.1)	>0.05	177.0 (−173.8–527.8)	>0.05
Maternal ferritin (S, µg/L)	−0.1 (−3.2–2.9)	>0.05	1.5 (−2.7–5.7)	>0.05	0.3 (−2.0–2.7)	>0.05
Maternal urinary creatinine (mmol/L)	−6.8 (−22.3–8.7)	>0.05	−13.8 (−31.1–3.4)	>0.05	−9.3 (−20.7–2.0)	>0.05
Maternal age	15.1 (−2.0–32.2)	>0.05	14.4 (0.75–29.5)	>0.05	14.8 (3.3–26.1)	<0.005
Smoking habits (see Table I)	34.6 (−165.1–234.3)	>0.05	−163.2 (−220.5–−5.97)	<0.005	−103.2 (−203.1–−3.3)	<0.025
Number of deliveries	83.1 (−22.1–188.3)	>0.05	37.7 (−32.5–107.9)	>0.05	54.9 (−4.7–114.4)	<0.05
Local food (yes/no)	−55.0 (−320.7–210.6)	>0.05	−62.6 (−218.8–93.5)	>0.05	−60.1 (−199.8–79.6)	>0.05
Maternal BMI (kg/m²)	13.7 (−9.2–36.5)	>0.05	23.4 (4.1–42.7)	<0.025	18.3 (3.3–33.2)	<0.005
Maternal height (cm)	−5.6 (−25.0–13.8)	>0.05	14.9 (0.6–29.1)	<0.05	5.4 (−6.5–17.4)	>0.05
Maternal weight (kg)	5.3 (−3.8–14.4)	>0.05	9.0 (2.7–15.4)	<0.005	7.4 (2.1–12.8)	<0.001
Pre-eclamptic condition (yes/no)	−118.3 (−359.2–122.7)	>0.05	1.16 (−301.1–303.4)	>0.05	−81.7 (−264.7–102.3)	>0.05
Country					399.1 (275.1–523.0)	<0.001

Table V. Influence of S-copper, S-zinc, S-selenium and S-ferritin on BMIC (weight/length²), grouped by quartiles, ANOVA

Element, grouped by quartiles	BMIC (s.d.) Group 1	BMIC (s.d.) Group 2	BMIC (s.d.) Group 3	BMIC (s.d.) Group 4	*p*-value[1]
Copper[2]	13.1	12.9	13.0	13.4	0.32
N=260	(1.6)	(1.8)	(1.8)	(1.8)	(0.38)
Zinc[3]	13.4	13.1	13.0	13.0	0.53
N=257	(1.9)	(1.6)	(1.8)	(1.8)	(0.52)
0.90					
Selenium[4]	12.5	13.3	13.1	13.4	0.03
N=257	(1.9)	(1.7)	(1.7)	(1.8)	(0.11)
Ferritin[5]	13.2	12.6	12.7	13.4	0.02
N=303	(1.9)	(1.8)	(1.8)	(1.8)	(0.01)

[1] *p*-values in parentheses refer to BMIC adjusted for gestational age.
[2] Concentration intervals; 16.1–30.9; 31.1–35.8; 35.9–40.4; 40.5–68.6 (μmol/L).
[3] Concentration intervals; 3.2–6.4; 6.6–7.8; 7.9–9.2; 9.3–16.5 (μmol/L).
[4] Concentration intervals; 0.51–0.98; 0.92–1.03; 1.04–1.17; 1.18–1.99 (μmol/L).
[5] Concentration intervals; 3–8; 9–15; 16–27; 28–245 (μg/L).

Table VI. Multivariate linear regression analysis model to predict birth weight for the combined Russian/Norwegian population[1]

Variable	Change in birth weight in g/unit of variable[2] (95% CI)	*p*-value
Copper (S)	3.3 (−8.7–15.2)	>0.05
Zinc (S)	−20.9 (−52.1–10.2)	>0.05
Selenium (S)	155 (−371–641)	>0.05
Ferritin (S)	0.3 (−2.9–3.4)	>0.05
Country	284 (88–479)	<0.005
Maternal urinary creatinine	−6.3 (−1.7–9.0)	>0.05
Maternal age	4.3 (−15.4–24.0)	>0.05
Maternal smoking	−45 (−182–92)	>0.05
Number of deliveries	30 (−67–127)	>0.05
Maternal body mass index (BMI)	18.9 (−1.4–39.2)	>0.05
Maternal height	16.4 (1.1–31.6)	<0.05

[1] Clinical variables chosen from Table III, based on strength of the regression coefficients or clinical interest. F-statistic for the model is 3.04, with d.f. 11 and 166, $p<0.001$.
[2] For units, see Table IV.

Analysis of variance by quartiles

Serum copper, zinc, selenium and ferritin concentrations when grouped by quartiles had no influence on birth weight, either for the separate countries or the whole material (data not shown). However, if we use BMIC as the outcome factor (adjusted or unadjusted for gestational age), we find that both selenium and ferritin are significant positive predictors ($p=0.002$ and $p=0.02$, respectively, Table V). A similar relationship between BMIC and zinc or copper could not be demonstrated. By contrast, grouping by quartiles showed that maternal urinary creatinine and birth weight were negatively correlated ($p=0.001$, unadjusted; $p=0.01$, adjusted).

Multivariate linear regression

The significant univariate and clinically significant parameters were put into a multivariate linear regression analysis (Table VI). In the model none of the essential elements turned out to be significantly correlated with birth weight. The positive predictive values of maternal BMI ($p>0.05$) and maternal height ($p<0.05$) were overshadowed by the substantial country factor ($p<0.005$). When employing birth weight adjusted for gestational age in the model, the contributions of BMI ($p<0.005$) and maternal height ($p<0.005$) were strengthened, while the country factor was weakened ($p>0.05$). Performing the same analyses with BMIC as the dependent variable produced no significant changes for copper, zinc and ferritin, while a positive correlation with selenium came close to significance [β-coefficient 1.02 (−0.3–2.3), $p>0.05$]. Further, BMI became a significant predictor of BMIC ($p<0.05$), the maternal height lost significance ($p>0.05$), and the country factor remained substantial ($p<0.001$). Gestational age adjustment had little impact in this instance. Gestational age adjustment restored the significance of maternal height ($p<0.05$), but had no other impact.

Discussion

Limitations of the study

Information for a number of the questionnaire responses (Table I) and delivery department data (Table II) are missing. This was difficult to prevent since at each hospital local midwives and gynecologists were involved. Unavoidable restrictions on serum collection, storage or shipment account for the reduced number of donors reported in Table III. Further, a number of information biases can be identified. Answers concerning the consumption of local food were not well answered in the Russian community of Monchegorsk. The reason for this may reflect the decision by the local interviewer not to emphasize this component. The refusal by 36% of the Russian respondents to provide information about alcohol consumption suggests that this topic is culturally sensitive. Even fewer individuals responded to educational background questions there. Inconsistency between interviewers is also of concern. However, this was unavoidable since so many different communities were involved. Furthermore, the questionnaire was translated from Norwegian into Russian and this may have affected some of the questions. Of course, inherent ambiguities in the questions may have influenced the consistency of the answers. In our judgment, the discrepancies between Norwegian and Russian physicians in classifying pregnancy complications and outcomes were minimal. An example is the diagnosis of the pre-eclamptic condition.

Selection bias might have occurred because of the transfer of cases with complications to regional hospitals. Patient transfers were few and three were recorded in total. Their omission did not affect the significance tests. Due to logistical and technical limitations, as well as economic reasons, the sample size for each country was too small to detect differences in the incidence of congenital defects. Much larger populations need to be examined to identify such outcomes with adequate statistical power, as they are relatively rare (15). The small number of cases identified in the present study is consistent with this.

Population characteristics and pregnancy outcomes

The most noticeable differences reported for the two comparison groups is the much higher prevalence of pre-eclamptic complications in Russia (Table I) and the substantially lower mean birth weight for the Russian neonates. The latter is also reflected in the lower mean BMIC. The birth weight has some disadvantages as a dependent variable for pregnancy outcome, due to genetic differences (16, 17). The body mass index of newborn children (BMIC) has been suggested to have some advantages as an index to the nutritional status of newborn children (18–20).

Serum copper, zinc, selenium and ferritin concentrations

It may be concluded from measurements of serum concentrations that the copper, selenium and iron (ferritin) statuses among both Russian and Norwegian mothers are adequate and similar (11). This is perhaps surprising as socioeconomic and nutritional conditions are quite different in the two countries.

Maternal serum copper concentrations are known to increase significantly in the second and third trimester of pregnancy (13, 21). This is implied in the end-of-term reference interval reported in Table III. Infections or inflammatory conditions also increase plasma or serum copper. Although copper deficiency is reported infrequently, it produces a plethora of clinical symptoms (13, 22), presumably because copper is an essential constituent of many enzymes and other important proteins (23). Good dietary sources are offal, especially liver, followed by seafoods, nuts and seeds (22).

The mean zinc concentrations found in both Russia and Norway fall well below accepted adult levels reported in the literature (10.8–22.9 μmol/L) (8, 11–14). Only in the non-arctic Norwegian city of Bergen did a substantial fraction of participants (68%) have serum zinc levels above the lower limit of this interval. It is known that pregnant women are at risk of acquired zinc deficiency because of its requirements by the developing fetus (13). Plasma or serum zinc is also hormonally suppressed during pregnancy. However, the rather low levels observed (c.f. values reported in 21) suggest that additional factors appear operative which are not necessarily related to nutrition. Possible examples are diurnal variations, stress, inflammation or infections. Zinc is needed for normal fetal development and is known to influence pregnancy outcome such as birth weight, as discussed in the next section. Although there has been some suggestion that iron-folate supplements reduce zinc absorption (13), the fact that the serum zinc concentrations are lower in both countries suggests that this is not a contributing factor since such supplements are not commonly prescribed in Russia. Since the iron, selenium and copper balances were in the normal range for both the Russian and Norwegian subjects, and since meats and/or seafoods are good sources of these elements as well as of zinc (22, 24), dietary deficiency is not very likely. Zinc is relatively poorly absorbed from whole grain products and their relative importance in the diet might furnish one explanation. Further research is no doubt required to verify the apparent low zinc status, especially in the arctic populations in our study, including the administration of a detailed food frequency questionnaire.

The serum selenium levels observed correspond well to those reported in other studies (3). It has been shown that serum selenium decreases slightly during pregnancy (13, 25). In Finland, including its arctic regions, there has been considerable concern about the low selenium content of foods grown on selenium deficient soils (26). Selenium supplementation of fertilizers has significantly improved the selenium status in Finland, as judged by serum concentrations (26). Since the observed serum selenium concentrations are in agreement with the international accepted intervals for adults (13, 14, 24, 26), we conclude that its status in both study groups is normal. Selenium is a component of a number of crucial enzymes and deficiency has been linked to cardiovascular disease and osteoarthritis in children; it is also suggested as a cancer risk (13, 24, 26). Seafoods, kidney, liver and to a lesser extent other meats, are reliable sources of selenium. By contrast, grains and other seeds as sources are considerably more variable, depending on the selenium content of the soils in which they have been grown (22).

Iron supplements for pregnant women in Norway may be considered routine (27). This practice is not in place in Russia. Despite this, the ferritin concentrations in the two countries were almost identical (p=0.8) and in the acceptable range. Serum ferritin in healthy women is a very appropriate indicator of the body's iron stores (28). Reference values have quite a wide range, and the current Norwegian accepted interval is 7–133 μg/L, depending on age, sex and pregnancy. Elevated serum ferritin in the second and third trimester has been suggested as a predictor of early spontaneous preterm delivery (29). Iron is widely distributed in the food supply; meat, eggs, fruits, vegetables, juices and cereals are the principal dietary sources. Absorption of iron is also very dependent on the iron status of the individual (13), as well as disease factors like liver disease and infections (28). Iron supplementation is recommended during pregnancy as well as foliate to assure proper erythrocyte development (22).

Birth weight as a pregnancy outcome

The univariate and multivariate regression analyses of birth weight (Tables IV and VI) suggest that maternal age, BMI, height, and weight, as well as number of deliveries, appear to be positive predictors of birth weight in the present subjects. On the other hand, maternal cigarette smoking and urinary creatinine concentrations are negatively associated variables. In addition, a large unknown country factor component dominates.

BMI is recognized as an age-dependent indicator of body fatness (30), although some residual dependence of this index on body height might be expected (31). Maternal age, BMI and height are indeed recognized predictors of birth weight (32, 33), as is parity (32, 34). As observed, maternal smoking is well known to suppress birth weight (32, 35). It is of interest that the 36% smoking frequency found among the Norwegian group (Table I), concurs almost exactly with the proportion of subjects identified as daily smokers prior to pregnancy in a recent survey of 4766 pregnant Norwegian women (36).

A positive association between maternal serum zinc concentration and birth weight after controlling for other determinants has been reported (37). Serum zinc levels <9.1 μmol/L late in pregnancy was associated with a 6-fold risk of a low birth weight infant; an increase of 1.0 μmol/L of serum zinc late in pregnancy corresponded to an increase of 56 g in neonatal weight. Interestingly, zinc supplementation during early pregnancy in women with relatively low plasma zinc concentration has been associated with greater neonatal birth weight and head circumference, being most effective in women with a BMI <26 kg/m^2 (38). Very low birth-weight infants also appear to respond with improved linear growth to zinc supplementation (39).

The positive correlations found between selenium and ferritin and BMIC, like that for zinc and birth weight, highlight the importance of good nutrition during pregnancy. Consistent with this is the work of Scholl et al. (40), who have shown that in low income, urban women use of prenatal multivitamin/mineral supplements have the potential to diminish infant morbidity and mortality. Godfrey et al. (41) have assessed the nutrient intakes of mothers in early and late pregnancy, suggesting that a high carbohydrate intake in early pregnancy suppresses placental growth, especially if combined with a low dairy-protein intake in late pregnancy. They postulated that this may have long term consequences for cardiovascular disease in offspring. A number of studies by the Barker group support such a hypothesis (42). A criticism of this view is that socioeconomic conditions at birth tend to persist throughout life, and appear to be more decisive for adult health than *in utero* undernourishment (43). A properly designed study of diet during pregnancy of Russian prospective mothers, which takes into account socioeconomic conditions, is clearly needed.

In the earlier publication (6), maternal urinary creatinine was a negative determinant of birth weight in both countries in a more restricted group drawn from the present study population. The linear regression and ANOVA results reported here corroborate this observation. Supporting evidence exists to interpret this parameter as an index to subclinical pre-eclamptic manifestations such as pregnancy induced hypertension (6, 44).

Concluding remarks

Even though we have identified a number of morphometric, clinical chemistry and life-style factors as determinants of birth weight or BMIC, the magnitude of the β-coefficient of the country factor in the univariate and multivariate analyses suggest we have failed to identify other important predictors of birth weight. In the first instance, this outcome presumably reflects unidentified differences in socioeconomic conditions not accounted for such as alcohol use, education and occupation (32, 33). Nutritional factors other than the essential elements considered, such as carbohydrate and protein intake during pregnancy, might also be relevant. Nevertheless, our positive findings for zinc, ferritin and selenium support the suggestion (19) that BMIC is somewhat more sensitive to the nutritional status of the newborn child than birth weight.

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PAPER III

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ORIGINAL ARTICLE

Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia

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Background. Delivering women and their newborns in the Kola Peninsula of Russia and the neighboring arctic area of Norway were studied to explore relationships between maternal cadmium and lead status and birth weight as a pregnancy outcome.

Methods. Life-style information, maternal blood and cord blood specimens were collected from 50 consecutive mother-infant pairs from hospital delivery departments in three Russian and three Norwegian communities. Pregnancy outcomes were verified by consulting medical records. Lead and cadmium were determined in the blood samples by electrothermal atomic absorption spectrometry.

Results. The median blood-cadmium concentration for the Russian mothers was 2.2 nmol/L ($n=148$) versus 1.8 nmol/L in the Norwegian group ($n=114$, $p=0.55$). A weak association was observed between maternal cadmium and amount smoked ($r=0.30$, $p<0.001$); no correlation was found between maternal blood cadmium and birth weight. The corresponding maternal lead values were 0.14 (Russia) and 0.06 µmol/L (Norway), $p<0.001$. The latter lead concentration constitutes one of the lowest adult population values reported to date. Maternal and cord blood lead levels were strongly correlated ($r=0.88$, $p<0.001$). In a multivariate linear regression model, maternal blood lead was recognized as a negative explanatory variable ($p<0.05$) for birth weight and child's body mass index (BMIC), with or without adjustment for gestational age. A similar association was suggested by ANOVA-analysis of maternal blood lead by quartiles.

Conclusion. Maternal blood-lead level as an environmental factor is an apparent predictor of low birth weight and BMIC. It reduced substantially the contribution of a country factor in explaining the observed differences in birth weight.

Key words: arctic populations; birth weight predictors; cadmium; environmental influences; lead; pregnancy outcome

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A number of publications have recently focused on the effect of environmental pollution and human health in the arctic areas of Norway and Russia (1–6). Although associations between occupational and environmental exposures to cadmium or lead and pregnancy outcome have been explored (7–10), no comprehensive studies exist that focus on environmental exposures in arctic areas. A prelimi-

Abbreviations.
AMAP: Arctic Monitoring and Assessment Programme; ANOVA: analysis of variance; BMI: body mass index; BMIC: body mass index of child; CBCd: cord blood cadmium; CBPb: cord blood lead; DL: detection limit; MBCd: maternal blood cadmium; MBPb: maternal blood lead.

This study was approved by The Regional Ethical Committee, University of Tromsø, Norway, the Norwegian Data Inspectorate and the Regional Health Administrations of Murmansk and Arkhangelsk Counties.

nary and incomplete report of concentrations of these toxic metals in biological fluids of pregnant women in the Norwegian and Russian arctic has appeared in conference proceedings (2). The full data complement and statistical analysis of maternal cadmium and lead status as possible risk factors for low birth weight and reduced BMIC are reported here.

Material

The Russian geographic sites in our study were Nikel, Monchegorsk, Kirovsk, Apatity, Murmansk and Arkhangelsk, while in Norway the cities were Kirkenes, Hammerfest and Bergen. Appropriate geographic and demographic information about these cities are provided in (11), including a map.

Information by questionnaire, maternal and cord blood were collected from 50 consecutive patients presenting themselves to the hospital delivery departments in each location. The registration and sampling were performed in the following time periods: Arkhangelsk in April–May 1993; Kirkenes, Hammerfest, Bergen and Nikel from November 1993 to June 1994. Maternal and cord blood were collected from a total of 262 mother/child pairs; of these 148 were Russian (Nikel, Monchegorsk and Arkhangelsk) and 114 were Norwegian (Kirkenes, Hammerfest and Bergen). A number of samples, especially from Kirkenes, had to be excluded because of storage or transportation difficulties. The women were asked to join the study by means of completing a consent form.

Methods

The personal, life style, morphometric and medical information was obtained through interviews and/or delivery department records, as described earlier (11).

Specimens of antecubital vein blood from the mother (immediately post partum) were taken in tubes (Sarstedt 02.264.020 10 ml Monovette, AH 23510) after installing a Viggo Spectramed venflon (1.4 mm, 17 Gauge L 45 mm) in the vena cubiti. Cord blood was collected by inserting the venflon into the cord immediately after delivery of the placenta, using the same equipment. The anticoagulant was heparin in both cases. The samples were immediately frozen at −20°C and kept frozen in isopor boxes during transport to the analytical laboratory; they were stored at −20°C until analysis.

Cadmium and lead in whole blood were determined by electrothermal absorption spectrometry (12), employing a Perkin Elmer Model 5100 PC/HGA-600 Zeeman-based absorption spectrometric system. Whole blood samples were first digested in hot nitric acid. The concentrations measured in whole blood quality-control materials (Nycomed, Norway) were in accordance with the values recommended by the manufacturer (±5%). The detection limits (DLs) were: 1.0 nmol/L for cadmium and 0.02 μmol/L for lead. Serum concentrations of copper, zinc, ferritin and selenium, as well as urinary creatinine and nickel levels, are known for most of the subjects (11, 13).

For the univariate analysis, multiple linear regression, and analysis of variance (ANOVA), the Epi Info and the SAS statistical software packages were employed (11). An association was accepted when the 95% confidence interval (CI) of the regression coefficient did not include zero. The Mantel-Haenszel and Fischer exact tests for comparison of proportions were used. The results of maternal blood lead and cadmium were not normally distributed, and the non-parametric Wilcoxon rank sum test or the Kruskal-Wallis test for two groups was used for comparison between groups. Concentrations below the DL were arbitrarily assigned the value of 1/2 DL. Birth weights corresponding to gestational ages 30–38 weeks were adjusted using the observed rate of increase of 166 g/week.

Results

Population characteristics and pregnancy outcomes

Population characteristics are presented in Table I. Maternal age and number of deliveries were higher in Norway, while the prevalence of pre-eclamptic

Table I. Population characteristics, Russia and Norway

Characteristic	Russia[a] (n=148)	Norway[b] (n=114)	p-value
Mean maternal age, years[c] (s.d.)	25.0 (5.8)	28.2 (5.1)	<0.001[g]
Mean number of deliveries[c]	1.2	1.5	0.003[g]
Mean body mass index (BMI; kg/m^2)	26.8	26.9	0.9[g]
Pre-eclamptic conditions[c,d] (%):	21.6	8.8	<0.001[h]
Smoking habits[e] (%):			
Non-smokers	76.4	63.2	0.01[h]
1–10 cigarettes/day	20.9	20.2	
>10 cigarettes/day	2.7	14.0	
Local food intake[e,f] (%):	83.1	50.9	<0.001[h]

[a] Arkhangelsk=50, Nikel=49, Monchegorsk=49.
[b] Kirkenes=19, Hammerfest=48, Bergen=47.
[c] Based on medical records.
[d] Pre-eclamptic conditions: hypertension, edema, proteinuria or anemia.
[e] Based on questionnaire.
[f] Regular use of locally produced vegetables, potatoes, berries and/or locally produced fish or meat.
[g] T-test.
[h] Chi-squared test.

Table II. Comparison between selected pregnancy outcomes in Russian and Norwegian populations

Pregnancy outcome[a]	Russian population (n=148)	Norwegian population (n=114)	p-value[b]
Mean birth weight, g	3178	3571	<0 001
(s.d.)	(616)	(488)	
Range	1400–5100	2150–4960	
Mean length of baby, cm	51.6	50.5	0 003
(s.d.)	(3.4)	(2.2)	
Mean body mass index of children, kg/m² (BMIC)	11.9	13.9	<0.001
(s.d.)	(1 7)	(1.3)	
Mean placenta weight, g	584	589	0 8
(s.d.)	(143)	(144)	
Mean gestational age, weeks	38.6	39 7	<0.001
(s.d.)	(2.0)	(1 4)	
Neonatal malformations[c] (%)	1 4	3 5	

[a] All information is derived from medical records. One perinatal death (the child with hydrocephalus in Arkhangelsk), but no still births in the period of data collection.
[b] T-test.
[c] Malformations: Russian group: 2 (1 hydrocephalus in Arkhangelsk, 1 minor heart defect in Monchegorsk). Norwegian group: 4 (2 limb defects, 2 minor heart malformations).

conditions and local food intake were higher in the Russian group. There was no difference in maternal BMI at term between the two countries. Smoking frequency was significantly higher in the Norwegian group.

Selected pregnancy outcomes are summarized in Table II. Birth weight was substantially lower in the Russian babies, as was BMIC. The mean gestational age also differed significantly (on average, 1.1 week shorter in Russia, $p<0.001$). Because of the very small number of reported cases, malformations at birth could not be statistically compared.

Whole blood concentrations of cadmium and lead

The cadmium and lead concentrations in whole blood and cord blood are presented in Table III for both the Russian and Norwegian participants.

Cadmium

The maternal blood cadmium (MBCd) levels were very similar in the two countries (p=0.55). Only three of the Russian values (2%) and four of the Norwegian results (2.4%) exceeded the suggested interval for non-smokers, all were smokers. Many of the cord blood cadmium (CBCd) results (89.6%) were below the DL, with one outlier at 38.6 nmol/L for which there was no corresponding maternal value. A correlation between maternal cadmium and cord blood cadmium was not observed, most likely because 73 MBCd- and 199 CBCd- values were below the DL.

Lead

Both the maternal (MBPb) and cord lead (CBPb) levels were higher in the Russian population than in the Norwegian subjects ($p<0.001$). In the Russian group, 39 values (23.4%) exceeded the reference level of 0.20 mol/L, while none did in the Norwegian group. Of the cord blood results, eight (4.8%) exceeded 0.20 mol/L and two exceeded the medical concern level for children of 0.48 µmol/L (17), all in Russia. The

Table III. Cadmium and lead concentrations in whole blood or cord blood of delivering women and their newborn children in the populations studied

Element	Russia median value (range)	Norway median value (range)	p-value[a]	Expected interval (14–16)
Cadmium (Whole blood, nmol/L)	2 2 (0 5–35 2)	1 8 (0 5–26 9)	0 55	<18 nmol/L (non-smokers)
n	148[b]	114[b]		
Cadmium (Cord blood, nmol/L)	0 5 (0 5–4 8)	0 5 (0 5–38 6)	–[d]	
n	98[c]	124[c]		
Lead (Whole blood, µmol/L)	0 14 (0 04–0 65)	0 06 (0 02–0 19)	<0 001	<0.20 µmol/L
n	148[b]	114[c]		
Lead (Cord blood, µmol/L)	0.10 (0.03–0 53)	0.05 (0.02–0.18)	<0 001	
n	98[c]	124[c]		

[a] Wilcoxon two-sample test.
[b] n=50 (Arkhangelsk); n=49 (Monchegorsk); n=49 (Nikel); n=47 (Bergen); n=48 (Hammerfest); n=19 (Kirkenes).
[c] n=49 (Arkhangelsk); n=0 (Monchegorsk); n=49 (Nikel); n=49 (Bergen); n=55 (Hammerfest); n=20 (Kirkenes).
[d] 89 6% of the values were at the DL, defined as 0 5 nmol/L

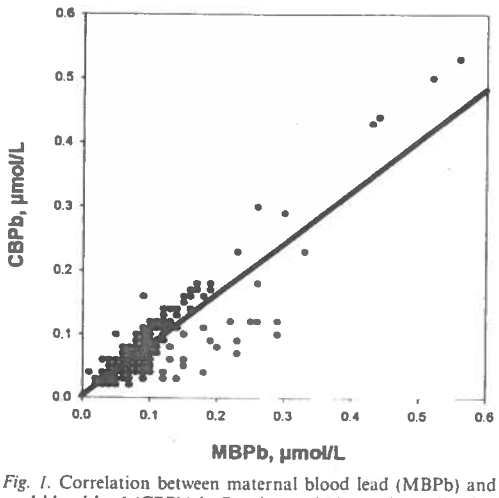

Fig. 1. Correlation between maternal blood lead (MBPb) and cord blood lead (CBPb) in Russian and Norwegian delivering women and their neonates; $n=222$, $r=0.88$, $p<0.001$.

correlation between cord lead and maternal blood lead was very strong ($r=0.88$, $p<0.001$, Fig. 1). There was a slightly negative, but insignificant association between serum selenium (11) and MBPb ($r=-0.16$, $p>0.05$).

Univariate linear regression and analysis of variance

The results summarized in Table IV illustrate the absence of any association between MBCd or CBCd concentrations and birth weight (or BMIC), consistent with the ANOVA of MBCd, grouped by quartiles (Table V). A significant, although weak, association between MBCd and amount smoked was evident ($r=0.30$, $p<0.001$). For non-smokers, no association was found between MBCd and serum selenium ($r=0.02$, $p>0.05$), while for the smokers there was a significant negative correlation ($r=-0.23$, $p<0.05$).

In the univariate linear regression (Table IV, footnote[a]), only BMIC was correlated with MBPb ($p<0.05$) in the Russian and combined groups when adjusted for gestational age; no such association was evident for CBPb. This finding is reinforced by the ANOVA when lead concentrations are divided by quartiles (Table VI, footnote[a]). The corresponding scatter diagram suggests that the data points corresponding to MBPb>0.48 µmol/L are outliers.

Table IV. Univariate linear regression analysis of birth weight. Weight change in g/unit (95% CI) and *p*-value

Variable	Russia	*p*-value	Norway	*p*-value	Both countries (adjusted)	*p*-value[a]
Cadmium (MBCd, nmol/L)	−11.5 (−32.5, 9.6)	>0.05	−9.9 (−26.7, 7.0)	>0.05	−10.7 (−24.3, 2.9)	>0.05
Cadmium (CBCd, mmol/L)	46 (−171, 262)	>0.05	−23.3 (−49.1, 2.5)	>0.05	−21.7 (−50.7, 7.4)	>0.05
Lead (MBPb, µmol/L)	−701 (−1646, 245)	>0.05	1339 (−1713, 4390)	>0.05	−583 (−1422, 256)	>0.05
Lead (CBPb, µmol/L)	−47 (−1513, 1419)	>0.05	−501 (−3679, 2677)	>0.05	−98 (−1304, 1107)	>0.05

[a] Comparable *p*-values were obtained when birth weight was adjusted for gestational age; when BMIC was the dependent variable, MBPb reached significance ($p<0.05$) in both the Russian and the combined Russian-Norwegian group when adjusted for gestational age.

Table V. Influence of maternal whole blood cadmium (MBCd, nmol/L) on birth weight, grouped by quartiles. ANOVA

MBCd, grouped by quartiles	Birth weight g (s.d.) Group 1 [conc. interval]	Birth weight g (s.d.) Group 2 [conc. interval]	Birth weight g (s.d.) Group 3 [conc. interval]	Birth weight g (s.d.) Group 4 [conc. interval]	*p*-value[a]
Russia ($n=148$)	3207 (561) [<0.5]	3214 (756) [0.5–2.1]	3214 (543) [2.2–3.6]	3109 (622) [3.7–35.2]	0.85
Norway ($n=114$)	3667 (552) [<0.5]	3508 (437) [0.5–1.7]	3486 (427) [1.8–5.7]	3482 (496) [5.8–26.9]	0.18
Total group ($n=262$)	3506 (595) [<0.5]	3364 (649) [0.5–1.9]	3260 (531) [2.0–4.4]	3339 (578) [4.5–35.2]	0.49[b]

[a] Comparable *p*-values were obtained when BMIC was the dependent variable and when adjusting for gestational age.
[b] Adjusted for country.

Table VI. Influence of maternal whole blood lead (MBPb, µmol/L) on birth weight, grouped by quartiles, ANOVA

MBPb, grouped by quartiles	Birth weight g (s.d.) Group 1 [conc. interval]	Birth weight g (s.d.) Group 2 [conc. interval]	Birth weight g (s.d.) Group 3 [conc. interval]	Birth weight g (s.d.) Group 4 [conc. interval]	p-value[a]
Russia	3323 (575)	3188 (723)	3253 (617)	2984 (493)	0.085
(n=148)	(<0.10]	[0.10–0.13]	[0.14–0.20]	[0.21–0.65]	
Norway	3578 (506)	3604 (532)	3496 (577)	3663 (439)	0.68
(n=114)	[<0.05]	[0.05–0.06]	[0.07–0.08]	(0.09–0.19]	
Total group	3552 (526)	3485 (564)	3288 (664)	3123 (562)	0.66[b]
(n=262)	[<0.07]	[0.07–0.09]	[0.10–0.15]	[0.16–0.65]	

[a] Comparable p-values were obtained when birthweight was adjusted for gestational age; when BMIC was the dependent variable, the indicated trend for the Russian data approached significance (p=0.055) and became significant (p=0.005) when adjusted for gestational age.
[b] Adjusted for country.

Multivariate linear regression

The independent variables tested (11, 13) using the backward stepwise regression approach (18) included: maternal age, BMI, height, serum zinc, urinary creatinine and MBPb; parity, pre-eclamptic condition, local food consumption and smoking. MBCd was also considered, since it might well serve as a surrogate for smoking. A final model that retains the important morphometric BMI for interest is summarized in Table VII. For unadjusted birth weight, MBPb is a negative predictor of birth weight ($p<0.05$), while maternal urinary creatinine as a risk factor and maternal age as a positive predictor are almost significant. When adjusting for gestational age, both maternal age ($p<0.05$) and BMI ($p<0.01$) are positive explanatory variables, with MBPb ($p<0.05$) a negative factor. An important feature of this model is the absence of a significant country factor.

The same multivariate analysis was also performed with BMIC as the dependent variable (see footnote[c], Table VII). Relative to birth weight, the impact of MBPb ($p<0.025$) and the unspecified 'country factor' ($p<0.001$) became stronger, with or without gestational age adjustment; no other factors in the multivariate model reached significance, except BMI ($p<0.01$) after adjustment.

Table VII. Multivariate linear regression analysis model to predict birth weight for the combined Russian/Norwegian population[a]

Variable for mother	Change in birth weight in g/unit of variable (95 % CI)	p-value[b, c]
Age (years)	14.7 (−0.9, 30.2)	>0.05
BMI (kg/m^2)	12.2 (−6.0, 30.4)	>0.05
Urinary creatinine (mmol/L)	−9.0 (−22.4, 4.3)	>0.05
Maternal smoking frequency (grouped, see text)	−42 (−183, 98)	>0.05
Blood lead (µmol/L)	−1068 (−2134, −2)	<0.05
Country factor (Russia/Norway)	179 (−40, 398)	>0.05

[a] Backward stepwise regression was employed which included all non-complementary variables that were significantly associated ($p<0.05$) with birth weight in previous work or in the current study (see text); overall p-value for the model is <0.001.
[b] When adjusting for gestational age, maternal age ($p<0.05$), BMI ($p<0.01$) and MBPb ($p<0.05$) were significant.
[c] Comparable p-values were obtained when BMIC was the dependent variable, with MBPb ($p<0.025$) and the country factor ($p<0.001$) exceptions; after adjustment for gestational age BMI was significant ($p<0.01$), as were MBPb ($p<0.025$) and the country factor ($p<0.001$).

Discussion

Context of the findings

Limitations of the study design and practical problems during sampling and transportation are discussed in two other papers by the authors (11, 13). In these papers, urinary nickel concentrations and essential elements in maternal serum are explored as possible explanatory variables for birth weight and BMIC. Maternal urinary creatinine and smoking were shown to have negative impacts on birth weight and BMIC, while maternal serum zinc, selenium and ferritin were shown to have weak positive influences. Morphometric explanatory factors that were positively correlated were maternal BMI, height and weight, as well as parity and maternal age. However, a significant, unidentified 'country factor' in the statistical models remained.

Maternal and cord blood cadmium concentrations

Blood cadmium concentrations of smoking Norwegian men have recently been shown to be comparable to values suggested previously for non-smoking persons (19). Because the observed levels of MBCd and CBCd are low, environmental sources of cadmium appear to have been minimal for both study groups. The significant correlation of MBCd to smoking suggests it may serve as a possible surrogate for smoking habits, as discussed also by other authors (7, 14, 19). Interestingly, Zenzes et al. (20) have shown that cadmium concentrations in follicular fluid of women undergoing *in vitro* fertilization-embryo transfer was higher in smokers. The significant negative relationship between MBCd and maternal selenium concentrations for the smoking mothers has been observed before for both adult smokers and non-smokers (19). Presumably, it reflects the involvement of selenium in cadmium metabolism or the existence of antagonistic dietary or life-style factors. For example, diets high in selenium circumvent cadmium toxicity in animals, perhaps by lowering cadmium uptake (14). Protein deficient diets (i.e., also low in selenium) are also known to increase the absorption of cadmium. Further, alcohol consumption by pregnant women depresses the cord blood selenium levels (21), and presumably also in the mothers.

Our results suggest a threshold for the passage of cadmium through the placenta. It seems that the human placenta serves as a selective barrier to cadmium with an average attenuation of 40–50% (22, 23). It might also be that individual variability related to metallothionein induction in the placenta is operative. The animal data support this conclusion, with free transport of cadmium through the Wistar rat placenta, while the hamster placenta is totally blocked (24, 25). Animal data suggest that oral exposure to cadmium results in reduced birth weight and more severe effects on the fetus, including placental damage (14). Evidence in humans of suppression of birth weight by cadmium is difficult to separate from the impact of smoking (14). Its main toxic effect in adults is on the kidney, producing tubular dysfunction characterized by enhanced excretion of renal tubular tissue enzymes, low-molecular-mass proteins, and other essential metabolites such as calcium and phosphate. Mild tubular dysfunction has even been associated with heavy smoking (26, 27).

Maternal and cord blood lead concentrations

The reason for the significantly higher lead concentrations in the Russian samples is probably the continued use of leaded gasoline (3). The low Norwegian cord blood levels are comparable to those reported for neonates born in the Faroe Islands (21), particularly if the mothers had frequently consumed fish or had abstained from smoking. In a parallel study by the present authors of indigenous peoples in the Russian and Norwegian arctic (3, 28), blood lead levels of children living in remote areas of the Kola Peninsula were shown to be near or above the level of medical concern for children of 0.48 µmol/L (17), significantly higher than in the urban populations of the Kola Peninsula. The reason for this is not obvious (28), but gun-powder fumes and the consumption of game contaminated with fragments of lead derived from leaded ammunition are hypothesized as likely sources (28, 29). Lagerkvist et al. (7) have done a study of arsenic, lead and cadmium concentrations in occupationally and environmentally exposed pregnant women in northern Sweden. The lead levels were higher in the occupationally exposed women, and increased during pregnancy. It is now apparent that pregnancy increases the mobilization of lead from maternal skeleton, thus increasing fetal exposure (30–32). The negative but weak relationship between MBPb and serum selenium concentration may well reflect the opposite relationship between those two parameters and alcohol intake (21, 33). As already indicated, alcohol consumption and serum selenium appear to be inversely related, while for blood lead it is direct.

The major environmental source of lead is the use of lead in gasoline. In the USA there has been a substantial decline in blood lead levels for persons aged 1–74 years from 0.62 µmol/L in 1976–1980, to 0.14 µmol/L in 1988–1991 and to 0.11 µmol/L in 1991–1994 (as geometric means), most probably because of the removal of lead from gasoline and soldered cans (34, 35). This reduction has also been demonstrated in Swedish children by Stromberg et al. (36). Other environmental sources of lead are industrial point sources, drinking water (from lead-soldered pipes) and lead-containing paints (17). The latter appears to constitute a major source of lead for children in the USA, even today (17, 35). The strong relationship between MBPb and CBPb confirms the free passage of lead through the placenta (37). There is no doubt that lead is a systemic poison, even at low to moderate blood concentrations (16, 17). The main environmental concern about lead is the impact on fetal development and neurodevelopment of the unborn and children, based on clinical and laboratory evidence (30, 38, 39). The blood lead concentration of medical concern (established threshold value) in children of 0.48 µmol/L is well below any action level for adults (17).

Dependence of birth weight on maternal blood cadmium and lead concentrations

Our results confirm that BMIC is an alternative to birth weight as an indicator of the health conditions of the newborn child (40–42). It appears to be especially useful as an index to nutritional status of the neonate (11). Interestingly, no studies of

BMIC and lead or cadmium exposure have been reported.

As in our own study, a connection between MBCd and birth weight independent of smoking is difficult to establish (e.g., 43). By contrast, smoking as a risk factor for low birth weight is clearly recognized (e.g., 44). Perhaps the relatively low smoking frequency among the Norwegian and Russian study populations contributed to the observation that smoking only occurred as a negative predictor in the univariate analyses (11, 13), but was not retained as such in the multivariate models that included essential elements (11) or toxic metals as parameters.

Andrews et al. (9) have critically reviewed the available epidemiologic studies on prenatal lead exposure in relation to premature rupture of membranes (PROM), preterm delivery, gestational age, low birth weight, mean birth weight and birth weight adjusted for gestational age. Many of the studies reviewed were vulnerable to community-related confounding factors, such as socio-economic status (45–47). Andrews et al. (9) conclude that: the association between PROM and prenatal lead exposure has not been confirmed, nor has that for preterm delivery and gestational age; by contrast, the data appear supportive of the hypothesis that prenatal lead exposure adversely effects birth weight and that this relationship may have a threshold (e.g., 48, 49). The birth weight finding showed some dependence on the method used in the statistical analysis. Consideration of gestational age did not clarify the relationships. Clearly, our own results support the conclusion by Andrews et al. (9) about the likelihood of an association of prenatal lead exposure and reduced birth weight, including the suggestion of a threshold (see Table VI).

The subjects of the present study, like those for whom maternal urinary nickel was examined as a predictor of birth weight (13), constitute a restricted subset of a larger population among whom the relevance of the status of essential elements was tested (11). In the urinary nickel and essential elements groups, maternal urinary creatinine did not quite reach significance as a predictor of low birth weight in both the univariate and multivariate linear regression analyses. The near significance of this parameter in the multivariate model in the present subset is therefore not an isolated observation. As described earlier (11, 13), there is evidence to consider maternal urinary creatinine as an index to subclinical pre-eclamptic manifestations such as pregnancy induced hypertension. Further, maternal age is a recognized determinant of birth weight (11), and thus its near significance in the present study is consistent with established findings.

In our studies, maternal nutritional status as a potential confounder has been assessed through mineral status and clinical/chemical parameters. Their importance is illustrated by a recent study suggesting that vitamin-mineral supplements during pregnancy suppress MBPb (45). Most studies, like ours, adjust for confounders through multiple regression analysis. However, variables, which are partly or indirectly determinants of lead exposure themselves, should not be regarded as confounders and need to be controlled for unequal distribution between study populations. Alcohol consumption, especially of wines, has been reported as a source of lead intake and as a confounding factor in the apparent relationship between smoking and blood lead levels (21, 33, 50). Perhaps more importantly, both alcohol consumption and smoking are known negative predictor variables of birth weight (51, 52). However, our lack of information about alcohol consumption and years of education in the Russian part of the material should not negate our multivariate model, but may have weakened our conclusion somewhat. Consequently, and contrary to the results of our multivariate model, smoking might still be an exogenous risk factor for low birth weight in our subjects. Differences in smoking habits between Russian and Norwegian pregnant women have decreased since our study was conducted (53, 54).

Concluding remarks

Clearly, birth weight or BMIC are complex pregnancy outcomes. Other explanatory variables not considered no doubt exist. One example may well be mercury, as methyl mercury in maternal blood has been observed to correlate inversely with birth weight. However, the results of a restricted sampling among our study population (n=60, Russia; n=25, Norway), indicated that the observed maternal blood, total-mercury concentrations found (2) were more than 20-fold lower than the methylmercury concentrations at which adverse effects on birth weight have been reported (55, 56).

The multivariate model presented in this paper points out a significant negative impact of MBPb concentrations on birth weight, even at concentrations regarded as safe for children. Its strong influence in reducing the importance of the known country factor in the multivariate analysis in explaining birth weight is intriguing. The observed β-coefficient (Table VII) of -1068 g (μmol/L)$^{-1}$ or 5 g (μg/L)$^{-1}$ is about 7-fold larger than the response reported by others (9, 46, 49). MBPb could be a surrogate variable for life style factors in Russia for which we have no information. Nevertheless, the rough agreement and the suggestion of a dose-response suggest that the apparent effect of MBPb on birth weight might be real.

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PAPER IV

Self-reported ethnic status of delivering women, newborn body mass index, blood or urine concentrations of toxic metals, and essential elements in sera of Norwegian and Russian Arctic populations

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ABSTRACT

As part of the Arctic Monitoring and Assessment Programme (AMAP), we assessed pregnancy outcome among Sami and Norwegian populations of Finnmark County in Norway and Russians living in the Kola Peninsula of Russia using body mass index of the newborn child (BMIC) as the main indicator; concentrations of essential and toxic elements in biological fluids of delivering women and their children served as additional sources of information. At the hospitals of Hammerfest and Kirkenes in the period November 1993 - June 1994 a total of 107 consecutive women gave birth to a child, of whom 15 regarded themselves as Sami. The Russian group (N=151) delivered their children in the same period. The Sami women were significantly older than the Russian group (28.5 versus 25.1 years, p=0.04). The mean birth weight was significantly lower in the Sami group compared to non-Sami Norwegians (p=0.01), but was of comparable magnitude to that recorded in Russia (p=0.4). For BMIC, the Sami and non-Sami Norwegian results were similar (p=0.2); both were significantly higher than in Russia (p<0.001). The essential elements copper, zinc, selenium and iron (as ferritin) in serum showed no differences between the groups, although relatively low levels of serum zinc were documented in all populations studied. Blood cadmium concentrations were strongly related to smoking frequency. Blood lead and urinary nickel levels were significantly higher for the Russian mothers, but did not reach levels of medical concern. *Conclusion*: No ethnic differences in concentrations of essential elements in biological fluids, nor of cadmium and mercury, were observed. However, national differences for lead and nickel were evident. Because of small sample size, these conclusions need confirmation. The similar BMIC values observed for the non-Sami Norwegian and Sami newborns, compared to the Russian group, suggest that BMIC may serve as a good indicator of the nutritional status and possibly also the general health condition of neonates. *(Int J Circumpolar Health 1999; 58: 4-13)*

One of the main goals of the Arctic Monitoring and Assessment Programme (AMAP) was to assess the living conditions of different indigenous groups living in arctic areas (1). Essential and toxic element status in biological fluids of pregnant women and their children living in arctic and subarctic areas of Norway and Russia, as well as possible effects on foetal development by the heavy industrial pollution in the Kola Peninsula, have been discussed by the present authors and others in several publications (2, 3, 4, 5, 6, 7, 8). The objective of the study reported here was to assess pregnancy outcome of women living in Finnmark County of Norway regarding themselves as Sami, compared to neighbouring non-Sami Norwegians (hereafter referred to simply as Norwegians) and Russian delivering women. Birth weight is a commonly used index for assessment of pregnancy outcome (9, 10). However, body mass index of the child (BMIC) has been suggested as a better parameter for evaluation of the nutritional status of the child (11, 12, 13, 14). Based on the cooperation established in the AMAP group, the study also included assessment of biological concentrations of essential and toxic elements in blood, serum or urine collected from the delivering women and their newborn children.

MATERIAL

This study was conducted as part of the first phase of AMAP, and details on enrolment and sampling procedures are described in the AMAP report (1) and the references cited in (2,3,6,7,8). The Sami population of Finnmark give birth to their children at the delivery departments of the Kirkenes and Hammerfest hospitals. The Kirkenes delivery department receives women from the eastern part of Finnmark (total population 28 000), the area geographically adjacent to the Russian border. The delivery department of the Hammerfest hospital receives women from the western part of Finnmark (a total of 45 000 residents), including the main native Sami centres.

Information by questionnaire, serum, whole blood, urine and placenta specimens were collected from a total of 107 consecutive patients presenting themselves to the hospital delivery departments, of whom 15 women regarded themselves as Sami. The enrolment and sampling were performed in the period November 1993 - June 1994. The women were asked to join the study by means of completing a consent form. None of the delivering women refused to join the study,

Table I. Population characteristics of delivering women of Finnmark County of Norway according to self-reported ethnic status, compared to Russian delivering women from the Kola Peninsula and Arkhangelsk.

Characteristic	Sami Population N=15	Norwegian Population N=81	Russian Population N=151	P-values N / S Groups	P-values R / S Groups
Mean maternal age, years[a]	28.5	27.4	25.1	0.7[e]	0.04[e]
(SD)	(5.4)	(5.6)	(5.8)		
Range	18-38	17-40	14-44		
Mean number of deliveries[a]	1.2	1.4	1.2	0.4[e]	0.9[e]
Range	0-3	0-5	0-4		
Mean height of mothers (cm)	164	166	163	0.7[e]	0.4[e]
Range	155-178	155-182	150-178		
Mean body mass index (BMI; kg/m^2)	26.3	26.1	26.9	0.2[e]	0.8[e]
Range	21.1-31.2	18.4-39.3	17.3-39.6		
Pre-ecclamptic conditions[a,c] (%):	6.7	9.9	21.2	0.7[f]	0.2[f]
Smoking habits[b] (%):					
Non-smokers	25.0	66.3	76.8	0.02[f]	<0.001[f]
1-10 cigarettes/day	50.0	21.2	20.5		
> 10 cigarettes/day	25.0	12.5	2.7		
Local food intake[b,d] (%):	86.7	69.1	83.4	0.2[f]	0.8[f]

a. Based on medical records.
b. Based on the questionnaire.
c. Pre-eclamptic conditions: hypertension, proteinuria or anemia.
d. Regular use of locally produced vegetables, potateos, berries and/or locally produced fish or meat.
e. T-test.
f. Chi-squared test.

but 11 women declined to answer the question about ethnic status. The study was approved by The Regional Ethical Committee, University of Tromsø, Norway, the Norwegian Data Inspectorate, and the Regional Health Administrations of Murmansk and Arkhangelsk Counties.

METHODS

In an interview, local midwives or gynaecologists administered a questionnaire to the expectant mothers to secure the following personal details: age, parity, height and weight of mother, schooling, occupation, smoking habits, alcohol consumption, medication, serious diseases before or during pregnancy and dietary habits related to local food intake. Delivery department derived information included Naegele term, date of delivery, length and weight of baby, weight of placenta, Apgar score, congenital malformations, gestational age, and individu-

Table II. Comparison between selected pregnancy outcomes in Sami and Norwegian populations in Finnmark County, compared to Russian pregnancy outcomes in the Kola Peninsula and Arkhangelsk.

Outcome[a]	Sami population N=15	Norwegian population N=81	Russian population N=151	p-values[c] N / S groups	p-values[c] R / S groups
Mean birth weight, g, (SD), range	3313 (478) 2735-4450	3634 (477) 2200-4925	3186 (612) 1400-5100	0.01	0.44
Mean length of baby, cm (SD), range	49.5 (2.1) 47-55	50.9 (2.0) 45-58	51.6 (3.4) 40-58	0.01	0.02
Mean body mass index of children (BMIC), (SD) range	13.5 (1.4) 10.2-15.8	14.0 (1.4) 10.1-19.4	11.9 (1.7) 7.5-18.2	0.2	<0.001
Mean placenta weight, g (SD), range	623 (135) 480-900	657 (157) 350-1050	585 (141) 300-900	0.5	0.4
Mean gestational age, weeks, (SD), range	39.3 (1.0) 38-41	40.0 (0.9) 38-42	38.7 (1.9) 30-52	0.02	0.2
Mean caput circumference, cm (SD), range	34.4 (1.6) 32-37	35.0 (1.5) 30-38	35.0 (1.5) 32-38	0.2	0.2
Neonatal malformations[b]	1	2	2		

a. All information is derived from medical records.
b. Malformations:
Sami group: 1 minor heart malformation
Norwegian group: 1 limb defect, 1 heart malformation
Russian group: 2 minor heart malformations
c. T-test.

al comments by the doctor or midwife. Enrolment, completion of the informed consent form and the questionnaire, and specimen collection were done before the delivery process started in order to minimize stress.

The sampling and analytical protocols for serum, blood and urine are described in detail by the authors (2, 3, 6, 7, 8), adhering to suitable quality control standards adapted by AMAP. For statistical assessment, the simple t-test was used in the case of normally distributed data, while the Wilcoxon signed rank test was selected for the data showing a skewed pattern. The Mantel-Haenszel and Fischer exact tests for com-

Table III. Comparison of different essential elements in maternal serum (S) of delivering Sami and Norwegian women living in Finnmark County of Norway and Russian mothers.

Element[a]	Norwegian Population	Sami Population	Russian Population	p-value[b] N/S Group	p-value[b] R/S Group	Suggested interval by end of pregnancy (15, 16, 17, 18)
Copper (S), µmol/L, mean	39.9	37.2	35.1	0.3	0.2	18.5-47.4
(SD)	(8.9)	(7.9)	(6.5)			
Range	22.3-68.6	27.6-53.1	18.5-57.0			
N	74	15	110			
Zinc (S), µmol/L, mean	7.0	7.5	8.2	0.3	0.1	10.8-22.9
(SD)	(1.7)	(1.3)	(1.7)			
Range	3.5-10.6	4.9-9.0	4.9-14.4			
N	74	15	107			
Selenium (S), µmol/L, mean	1.0	1.0	1.0	0.9	0.8	0.7-1.6
(SD)	(0.2)	(0.2)	(0.2)			
Range	0.5-1.4	0.7-1.3	0.6-1.6			
N	74	15	108			
Ferritin (S), µg/L, mean	23.0	32.9	23.5	0.1	0.3	7-133
(SD)	(22.1)	(16.9)	(33.8)			
Range	5-157	9-167	3-245			
N	78	14	150			

a. The detection limits (DL) were : 0.08 (Cu), 0.1 (Zn), and 0.04 (Se) µmol/L.

b. T-test

parison of proportions were also employed.

RESULTS

The population characteristics of the two groups are shown in Table 1 and include those for a comparable Russian group in the AMAP study. The latter group includes pregnant women and their neonates from the industrial cities of Nikel (23 000 inhabitants) and Monchegorsk (65 000 inhabitants) in the Kola Peninsula and the subarctic city of Arkhangelsk (419 000 inhabitants). In the Norwegian group (N=107), 11 women (10.3 %) refused to answer the question about self-reported ethnic status; 15 women (14.0 %) regarded themselves as Sami. The maternal characteristics were very similar in the Norwegian and the Sami groups, with a higher smoking frequency among the Sami group as the only significant difference (p=0.02). Compared to the Sami study group, we found the Russian delivering women to be significantly younger, the incidence of pre-eclamptic complications higher in Russia (but not reaching significance, p=0.2), and the smoking frequency significantly lower (p<0.001).

Table IV. Comparison of difference toxic elements in maternal whole blood (WB), cord blood (CB), maternal urine (MU), and children's urine (CU) of delivering Sami and Norwegian women living in Finnmark County of Norway, and comparable Russian populations living inthe Kola Peninsula and Arkhangelsk.

Element[a]	Norwegian population	Sami population	Russian population	p-values[b] N/S groups	p-values[b] R/S groups	Suggested end of pregnancy intervals (19, 20, 21, 22, 23)
Cadmium (WB)						
nmol/L, median, range	2.3	1.4	2.2	0.7	0.8	<18 nmol/L
N	0.5-22.3	0.5-12.8	0.5-35.2			non-smokers
	52	10	148			
Cadmium (CB)						
nmol/L, median range	0.5	0.5	0.5	All below	0.2	
N	0.5-0.5	0.5-0.5	0.5-4.8	DL		
	59	11	98			
Lead (WB)						
µmol/L, median range	0.06	0.06	0.14	0.6	<0.001	<0.20 µmol/L,
N	0.02-0.15	0.03-0.10	0.04-0.65			level of medical
	52	10	148			concern 0.48 µmol/L
Lead (CB)						
µmol/L, median range	0.06	0.04	0.10	0.1	<0.001	Level of medical
N	0.02-0.16	0.03-0.09	0.03-0.53			concern 0.48 µmol/L
	59	11	98			
Mercury (WB)						
nmol/L, median range	12.5	11.0	8.0	0.3	0.3	<12 nmol/L
N	4.0-20.0	9.0-12.0	2.0-22.0			
	20	5	56			
Nickel (MU)						
nmol/L, median range	4	14	85	0.1	<0.001	8.5-104 nmol/L
N	4-82	4-78	4-2108			
	73	12	149			
Nickel (CU),						
nmol/L, median range	4	4	34	0.5	<0.001	
N	4-48	4-34	4-561			
	72	14	137			

a. DL values were : 0.02 µmol/L (Pb), 1.0 nmol/L (Cd) and 8 nmol/L (Ni). Values below DL defined as ½ DL for statistical purposes.
b. Wilcoxon Two-Sample Test

The delivery outcomes are shown in Table II. The Sami neonates have significantly lower birth weight (p=0.01), length (p=0.01), and gestational age (0.02) compared to the Norwegian babies. BMIC is, however, very similar in the two populations (p=0.2). Comparing the Russian and Sami groups, BMIC is significantly lower in Russia p<0.001) and the babies are longer at birth (p=0.02). The Russian and Sami children have very similar birth weights (p=0.44). BMIC is also significantly lower in the Russian group compared to the Norwegian study population (p<0.001).

The essential elements copper, zinc, selenium and ferritin show no significant differences in any of the groups (all p values >0.05, see Table III). However, the maternal serum zinc levels in the Sami, Norwegian and Russian groups are low compared to known reference intervals at term.

The concentrations of cadmium, lead and mercury in blood and nickel in urine are shown in Table IV, with no significant differences between the Sami and Norwegian groups. There was a substantial range in the cadmium levels in all groups, the highest values clearly related to the mother's smoking frequency ($p<0.001$). The cord blood concentrations of cadmium were mostly below DL. The lead concentrations found were low and a strong correlation was exhibited between maternal and cord blood concentrations ($r = 0.88$, $p <0.001$). The maternal blood mercury concentrations were in the expected range for moderate fish eaters in both groups (2, 22). Urinary nickel levels were mostly at the DL for Finnmark mothers (Sami and Norwegian). However, among the Russian groups, blood lead levels and urinary nickel levels were significantly higher ($p<0.001$ and $p<0.001$, respectively).

DISCUSSION

The ethnicity identification in this study is based on the self-reported ethnic status (24). Although other indicators, including DNA markers, have been used in other studies, all have inherent uncertainties (24, 25, 26, 27). The outcome predictors described must be interpreted with caution because of the very few deliveries recorded for Samis in Finnmark County. Congenital malformations are almost impossible to assess in the relatively small groups considered (9). Birth weight depends on several factors, including genetic attributes (28, 29). Compared to Norwegians, the mean birth weight is significantly lower in the Sami and the Russian group, with no difference between the latter ($p=0.2$). In 1986, Forsdahl (30) discussed standard tables for height and weight, and found only that W/H^2 and W/H^3 suitably defined BMI for Scandinavian people. Relative to Sami babies, the BMIC in the Russian group is significantly lower ($p<0.001$). In other studies, the Ponderan Index and the Benn Index have been discussed as alternative indices of the nutritional status of the newborn child (12, 13, 14, 32). Ponderan Index and Benn Index correlate almost exactly to BMIC in our study ($r=0.93$, $p<0.001$, and $r=0.92$, $p<0.001$, respectively).

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When we used BMIC as the dependent variable in a regression analysis instead of birth weight, correlations with the essential elements are generally strengthened, suggesting that BMIC might indeed be a better indicator of the health condition of the newborn child (7). The Sami group of Finnmark County has probably comparable social and economic conditions and pregnancy care compared to the Norwegian group, while the Russian communities generally experience poorer social and economic environments and likely receive less effective care when pregnant.

The authors have in other papers discussed essential and toxic elements in connection to pregnancy outcome among arctic Norwegian and Russian populations (6, 7, 8). Unfortunately, comparable indigenous populations of northern Russia were not possible to include at the time of sampling. The serum concentrations of essential elements among the Sami group identified fall into the same concentration range as the Norwegian and Russian groups. Copper levels are shown to increase during pregnancy (33) and selenium levels will slighty decrease in normal pregnancies (34). Enhanced ferritin concentrations have been connected to hypertensive complications and premature deliveries (35); of course its deficiency reflects poor iron status which is to be avoided in pregnant females. Maternal zinc concentrations are shown to decrease significantly during pregnancy (33). The authors have shown Norwegian and Russian end of pregnancy zinc values to be lower than observed elsewhere (36). Further studies which are more focused on nutrition and dietary habits must obviously be initiated to find out if this finding represents a health problem or if it is a picture of a normal situation in arctic areas (37, 38). Scholl et al (39) have shown that the impact of multivitamin/mineral-supplementation can be very positive for the pregnancy outcome under depressed socioeconomic conditions. Other than for zinc, the values observed for copper, iron and selenium in serum for the Sami group are in the normal range when taken into account the physiological changes during pregnancy.

Cadmium in maternal blood correlated significantly with smoking habits ($r=0.34$, $p<0.01$), independent of ethnic status ($r=-0.09$, $p>0.05$), and the lack of correlation between maternal blood cadmium and cord blood cadmium suggests a barrier for cadmium in the placenta ($r=-0.01$, $p<0.05$) at the low levels observed (40, 41). Other studies indicate only a partial placenta barrier for cadmium, depending on concentrations (42, 43). The increased smoking frequency in the Sami group compared to the Norwegian group in our study (7, 44) con-

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forms to studies of other indigenous groups living in the arctic or at northern latitudes (1, 45).

The lead levels of the Sami group are indistinguishable from the Norwegian levels (p=0.6), and reflect the low levels shown by Grandjean et al in the Faroe Island Study (45). The results confirm the free flow of lead through the placenta (43). The higher concentrations shown in the parallel Norwegian-Russian study are probably connected to the continuing use of leaded gasoline in Russia (1, 46, 47). However, as noted in the AMAP Report (1), blood lead concentrations of native schoolchildren living in remote areas of the Kola Peninsula (Sami and Komi) were surprisingly high, up to and exceeding the level of medical concern for children (1, 21, 48). The reason for this finding still remains unresolved, and must obviously be further explored. One possible explanation is the use of leaded ammunition in subsistence hunting (48, 49).

Urinary nickel concentrations in the Norwegian and the Sami group are mostly at the detection limit (DL). The significantly higher concentrations in the Russian mothers and newborns independent of vicinity to nickel smelters, point out other sources for biologically available nickel (6, 50), like diet, nickel in mouth prosthesis or cooking utensils (51).

The mercury levels found in most of our cases fall into the group of "moderate fish consumers". Brune et al (22) report ranges of <21 nmol/L for non-fish eaters, 12-36 nmol/L for eating <2 fish meals/week, and 13-412 nmol/L for 2 fish meals weekly; one fish meal corresponds to approximately 200 g fish. We have, however, too few cases in our study to assess the body burden of mercury in the Sami population (N=5).

CONCLUDING REMARKS

The concentrations of both toxic and essential elements in biological fluids fall into national/geographic patterns, with no apparent ethnic differences. The agreement between the BMIC of the Norwegian and Sami newborns, and the significant difference in this parameter between the Sami and Russian groups, support the notion that BMIC is a good indicator of the nutritional status and possibly also the general health condition of the newborn child. Correlations to nutritional status and environmental factors have been noted in other studies by the authors, which also suggest that social and economic aspects of the general society are important. Because of the limited numbers, the research described should be followed-up with a more comprehensive study that includes

Russian indigenous populations and which focuses on pregnancy care, including dietary habits and life-style issues during pregnancy.

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PAPER V

RESEARCH AND APPLICATION

▼

Elevated Blood Lead Concentrations in Children Living in Isolated Communities of the Kola Peninsula, Russia

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ABSTRACT

Lead levels were determined in children aged 5–14 in three communities: two groups (N = 24 and 39) from Apatity, an industrial city, a group (N = 47) from Lowozero, an isolated Saami village, and another (N = 14) from Krashnochelie, a remote native village with Sami, Komi, and Nenets populations. As in the northwestern James Bay region of Canada, unexpectedly high blood lead concentrations were found in the most isolated community, namely Krashnochelie. The median lead concentration in Krashnochelie was significantly higher ($p < 0.01$ or $p < 0.02$) than those for the other village and city. In the Krashnochelie group, the lead levels were not gender dependent. The percentage of children with blood lead concentrations at or above the medical concern level of 0.48 μmol/l was highest (36%) in Krashnochelie, compared to 8% in Apatity and 6% in Lowozero. All but two of the 124 individuals tested had ferritin concentrations above that indicative of depleted iron stores (10 μg/l for age <14 years); the median ferritin values were comparable for all four communities. Iron status differences can therefore not explain the elevation of blood lead concentrations in the Krashnochelie group. A number of explanations are provided to account for the implied differences in lead exposure in the four study groups.

INTRODUCTION

Recent publications have presented evidence for: (1) the accumulation of lead in wildfowl skeletal muscle as fragments or pellets (Tsuji *et al.* 1999); (2) lead pellet ingestion in First Nation Cree of the western James Bay region of northern Ontario, Canada (Tsuji & Nieboer 1997); and (3) for the elevation of lead in teeth of adults (Tsuji *et al.* 1997) and in deciduous teeth of children (Tsuji, unpublished) living in the same isolated northern Ontario communities. Furthermore, an infant feeding study in the same region has indicated that cord and maternal blood lead concentrations correlated with the consumption of a traditional diet of game (fowl and mammal) (Hanning *et al.* 1996, 1997). Collectively, these observations suggest that wild meat can be a significant source of lead exposure in adults and during prenatal development. Consistent with this hypothesis is that blood lead concentrations in native children of the James Bay region have in the past exceeded those in children living in larger northern On-

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tario urban centers (OMHE 1989). In a more recent survey, the blood lead levels in these native children were somewhat lower but still comparable in magnitude to values in groups of similar age living in southern Ontario urban centers (OMH 1993). The general lowering of lead blood in many countries is known to parallel changes in population-wide lead sources such as the removal of alkyl-lead antiknock agents from gasoline and lead from soldered cans (Brody *et al.* 1994; Pirkle *et al.* 1994).

As a component of an extensive study of essential and toxic elements in pregnant mothers and their newborns in the Kola Peninsula of Russia (Odland *et al.* 1996, 1997), lead concentrations were also determined in the blood of children in a few communities. This was done to ascertain, by analogy to the Ontario Canada experience, whether Russian children living in isolated native communities were at higher risk of lead exposure than non-native children living in more urban areas. It was hypothesized that an environmental factor rather than low iron status might be responsible for the anticipated blood lead elevation in the native communities. It is well known that anemia is a risk factor for enhanced lead absorption (Mahaffey 1990; Sargent 1994; IPCS 1995).

This study was approved by The Regional Ethical Committee, University of Tromso, Norway, the Norwegian Data Inspectorate, and the Regional Health Administration of Murmansk County, as well as the local health authorities in Apatity and Lowozero (including Krashnochelie) communities.

SUBJECTS

Personal contacts with colleagues in the local children's polyclinics were established in the towns of Apatity, Lowozero, and Krashnochelie (Figure 1). Apatity (70,000 inhabitants) is a significant industrial centre for the mining of apatite and is part of a mineral-based corridor between Murmansk and Kandalaksia (see Figure 1). Lowozero (5000 inhabitants) is located 80 km east of this industrial corridor and most of its people are Sami. Krashnochelie (800 inhabitants) is located 150 km east/southeast of Lowozero at the river Ponoi and is a native village with mainly Sami, Komi, and Nenets peoples. It has no road access. Blood samples were collected from 65 children in Apatity, 50 in Lowozero, and 14 children in Krashnochelie (corresponding to most of the children in the age group 3–8 years). Group characteristics are provided in Table 1. There were two separate collections in Apatity, one in March 1995 (Apatity 1) and a supplemental collection in November 1995 (Apatity 2) to replace specimens lost in transit. Samples in Lowozero and Krashnochelie were obtained in April 1995.

ANALYTICAL DETAILS

Samples of antecubital vein blood were taken in tubes (Sarstedt 02.264.020 10 ml Monovette) tested to be free of lead (≤0.02 µmol/l) after installing a Viggo Spectramed venflon (1.4 mm, 17 Gauge L 45 mm) in the vena cubiti. Whole blood was immediately frozen at −20°C at the local hospital, while serum was centrifuged and transferred to tubes (Sarstedt 127-4004) for storage at −20°C. After each field trip, samples were immediately transported frozen to Norway, and kept at −70°C until analysis. A 2.5 ml volume of subdistilled 65% nitric acid (Chemscan, Elverum, Norway) was added to 2 ml of whole blood in a propylene digestion tube. After degasification at room temperature overnight, the tube was heated at 95°C for 1 hour in a laboratory oven. The samples were allowed to cool to room temperature before final dilution to a previously calibrated volume (13.7 ml). Lead was measured by electrothermal atomic absorption spectrometry (Welz *et al.* 1992) using a Perkin Elmer Model 5100 PC/HGA 600 system equipped with a Zeeman-based background correction system (Bodenseewerk Perkin-Elmer GmbH, Überlingen, Germany). The spectrometer was calibrated with whole-blood matched-standard solutions. The accuracy and reproducibility of the measurements were assessed continuously by using human whole blood quality control materials (STE 404107) obtained from Nycomed Ltd. (Oslo, Norway). The day-to-day variation of the lead in this quality control material was 8% at an observed average lead concentration of 0.16 µmol/l, which corresponds to the recommended value. The detection limit of the method was 0.02 µmol/l of lead. The ferritin in serum was measured by a Hitachi 917 autoanalyzer using a standard kit (Boehringer-Mannheim, Mannheim, Germany) and a routine analytical protocol.

For statistical analysis, the Epi Info, Version 6.04a (WHO 1996) was used. All statistical calculations were automatically tested for homogeneity of variance (Shapiro-Wilk's test for normality or Bartlett's test for homogeneity of variance). Lead

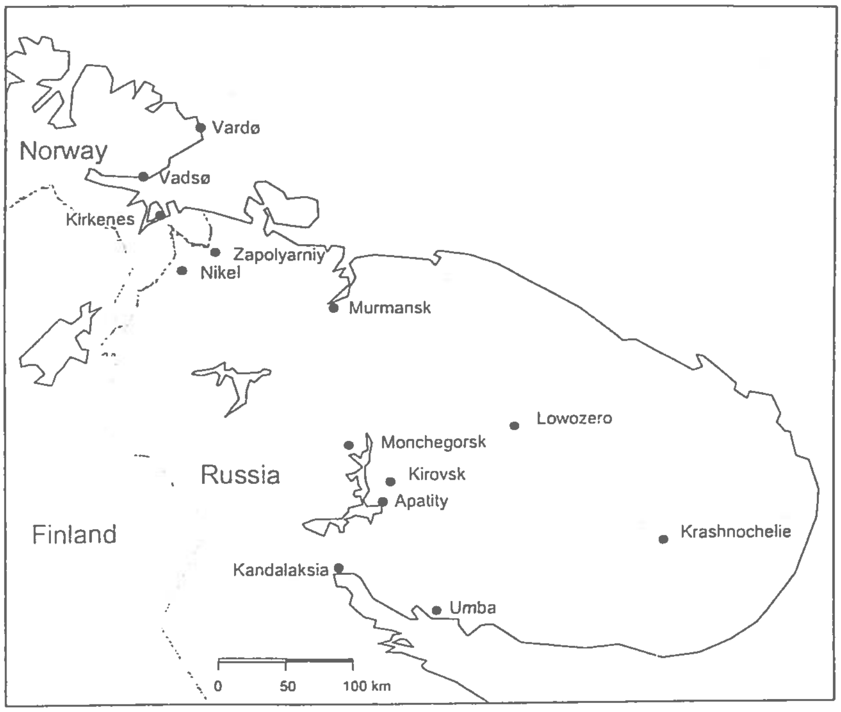

FIGURE 1. Map of the Kola Peninsula showing major locations and adjoining areas. With courtesy of Harvey Goodwin, Akvaplan-Niva, Tromsø, Norway.

and ferritin failed the parametric criteria and nonparametric tests were employed. Blood lead data for the two Apatity age groups and for the boys and girls from Krashnochelie were combined since they were not significantly different (Kruskal–Wallis test for two groups of unequal size, $p = 0.76$ and 0.95, respectively). A similar conclusion applied to the ferritin data in both instances ($p = 0.14$ and 0.27, respectively). Between-group comparisons for both parameters were examined by the Kruskal–Wallis One Way Analysis of Variance test for two groups.

RESULTS

The observed concentrations of blood lead and serum ferritin are summarized in Table 1; for lead they are also depicted graphically in Figure 2. Blood lead concentrations were not significantly different between Apatity and Lowozero and were lower ($p < 0.02$) than those observed in Krashnochelie. For the latter group, the lead levels were not gender dependent (see Table 1). It is evident from the graphical presentation in Figure 2 that the percentage of children with lead concentrations at or above the medical concern level of 0.48 μmol/l (CDC 1991) was the highest (36% or 5/14) in Krashnochelie, compared to 8% in Apatity (5/65) and 6% in Lowozero (3/50).

Ferritin concentrations were in the normal range, although in two cases they were below the concentration indicative of depleted iron stores (10 μg/l for age <14 years) (Borch-Iohnsen 1995; RiTo 1995). One boy in the Apatity 2 group had ferritin at 8 μg/l and a corresponding blood lead of 0.20 μmol/l, while for one boy in the Lowozero group it was 6 μg/l with lead at 0.27 μmol/l. The median ferritin value for the older boys in Apatity (Group 2) was significantly lower than the concentrations observed in Lowozero ($p < 0.02$; see Table 1). There was no correlation between lead and ferritin concentrations ($r = 0.07$, $p > 0.05$), nor between lead and age ($r = -0.12$, $p > 0.05$).

TABLE 1

Lead and ferritin concentrations in blood of Russian children

Group[1] (Mean age; range)	*Blood Lead (µmol/l)* Mean ± SD	Median	Range	*Serum Ferritin (µg/l)* Mean ± SD	Median	Range
Apatity 1 boys, N = 39 (6.2; 5–8)	0.28 ± 0.22	0.21[2]	0.11–1.42	33 ± 10	34	13–59
Apatity 2 boys, N = 24 (11.0; 10–12)	0.24 ± 0.12	0.23[2]	0.07–0.55	28 ± 13	26[4]	8–51
Lowozero boys, N = 47 (9.4; 4–14)	0.28 ± 0.11	0.25[3]	0.10–0.60	38 ± 18	33	6–105
Krashnochelie N = 14 (5.4; 3–8)	0.40 ± 0.18	0.40	0.10–0.76	33 ± 12	33	16–56
boys, N = 8	0.40 ± 0.23	0.42	0.10–0.76	30 ± 11	31	16–48
girls, N = 6	0.39 ± 0.12	0.37	0.25–0.54	37 ± 14	37	22–56

[1]N-values correspond to subjects for whom both lead and ferritin concentrations were measured.
[2]Significantly different from Krashnochelie at $p < 0.01$, but not from each other.
[3]Significantly different from Krashnochelie at $p < 0.02$.
[4]Significantly different from Lowozero at $p < 0.02$

DISCUSSION

The observed lead concentrations are lower than the values seen in the past in Europe or North America (e.g., a geometric mean, GM, of 0.71 µmol/l for ages 1–5 during 1976–1980 in the U.S., Pirkle *et al.* 1994), but higher than more recent results (e.g., GM of 0.17 µmol/l for ages 3–5 and of 0.12 µmol/l for ages 6–11 during 1988–1991 in the U.S., Brody *et al.* 1994; and GM of 0.13 µmol/l for ages 1–5 and 0.092 µmol/l for ages 6–11 during 1991–1994 in the U.S., CDC 1997). Interestingly, the mean lead level of 0.40 µmol/l for the Krashnochelie children is comparable to that reported recently (Factor-Litvak *et al.* 1998) for youngsters aged 4.5–9.5 years living in Pristina, Kosovo, a sizeable town without apparent industrial emissions of lead. As indicated earlier, the prevalence among Krashnochelie children with blood lead ≥0.48 µmol/l was 36%. This is considerably higher than the highest prevalences reported in the United States during the period 1988–1994, respectively, 20% for non-Hispanic black children ages 1–5 years living in old housing, and 28% among those of the same ages from low-income families (Brody *et al.* 1994; CDC 1997). Since the Krashnochelie children were only slightly younger than those in Apatity 1 and nearly spanned the same ages, and no detectable age-dependence was observed for the blood leads for all subjects or individual groups, we believe that the high prevalence of elevated lead concentrations in Krashnochelie reflects a unique exposure source. Although each community except Apatity was only sampled once, it is unlikely that this introduced random factors such as travel to areas with extensive industrial lead pollution. First because of long distances between arctic communities, limited transport, and the timing of the collections within the school year, nonlocal travel was not common. Second, since the half-life of lead in the peripheral blood compartment is relatively long (around 1 month; Skerfving *et al.* 1995), the timing of sample collection is not too critical.

The most common sources of lead exposure experienced by U.S. children are dust and chips derived from lead-based paint as well as soil and dust contaminated with residual lead fallout from vehicle exhaust (CDC 1991, 1997). In the Kola Peninsula, as elsewhere in Russia, most people live in similar municipality-owned apartments built in the 1960s or later that have comparable playground facilities. This applies to the residents of Apatity and Lowozero, but not of Krashnochelie. No differential residence-related exposure can therefore be attributed to the children living

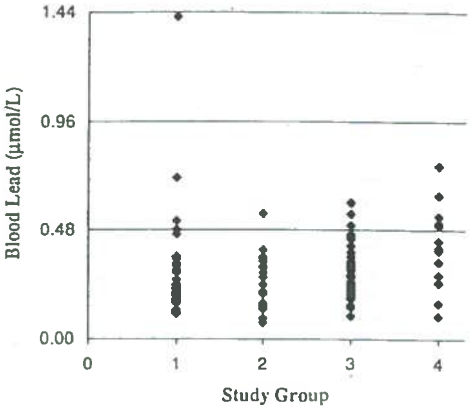

FIGURE 2. Distribution of blood-lead concentrations relative to the medical level of concern of 0.48 µmol/l (see text). The study groups are: 1, Apatity 1; 2, Apatity 2; 3, Lowozero; 4, Krashnochelie.

in Apatity and Lowozero. By contrast, the housing in Krashnochelie consists of wooden cabin-like structures without inside plumbing and minimal use of interior or exterior paint.

It is unlikely that lead-based paint accounts for the elevation of blood leads seen in this community. However, lead additives are still used in gasoline in Russia, although it should be pointed out that automobile ownership is low in Russia compared to Europe or North America. Based on the extent of urbanization and the associated increased traffic density, one would expect the blood lead concentrations to be the highest in the Apatity groups followed by Lowozero. As already indicated, Krashnochelie is a very isolated community with no road access, and thus has very low traffic density. It is clear from the blood lead data in Table 1 that the predicted pattern based on automobile emissions is not observed. Further, since serum ferritin is accepted as a suitable measure of a person's iron status (Borch-Iohnsen 1995), the data in Table 1 provide good evidence that the iron balance is normal in all three communities as the observed concentration ranges are consistent with the accepted reference interval of 7–140 µg/l for children 6 months to 15 years of age (Burtis & Ashwood 1996). Interestingly, the child with the lowest ferritin concentration (6 µg/l) in Lowozero had a moderately low lead value (0.27 µmol/l); the same was true in the Apatity 2 group with values of 8 µg/l and 0.20 µmol/l, respectively. Thus iron status is not an explanatory variable for the relatively high lead levels in Krashnochelie.

As indicated in the introduction, the trend suggested in this study that members of indigenous communities have higher blood lead concentrations than nonindigenous individuals has been observed in northern Ontario, Canada. Very recently, similar findings are reported for cord-blood lead concentrations among Inuit and a nonindigenous comparison group, as well as for blood lead in adults (AMAP 1998). The major source of lead for adult Inuit living in northern Canada or Greenland was assigned to food items of marine origin (ringed seal, narwhal, walrus, and beluga). Traditional foods in which waterfowl is a major food item have also been correlated with lead concentrations in maternal and cord blood (Hanning *et al.* 1996, 1997). Generally speaking, lead levels in arctic fish, marine mammals, and sea birds are low and differences between tissues are not apparent (AMAP 1998). Tissue-bound lead is therefore likely only a minor dietary source. However, contamination of tissues with lead pellets or microsize lead fragments for animals shot using leaded-ammunition is recognized, especially for waterfowl (Hubbard *et al.* 1965; Frank 1986; Scheuhammer & Norris 1995; AMAP 1998; Tsuji *et al.* 1999). As already indicated, radiographic evidence of lead shot in the gastrointestinal tract of native people who regularly eat game has confirmed ingestion. There is also some evidence that lead in pellets and fragments in meats from wildlife harvested with leaded ammunition is biologically available. Madsen *et al.* (1988) reported an increase in blood concentrations, relative to controls ($p < 0.02$), in individuals with lead shot retained in their appendix. As there are no obvious point or readily apparent residence-related sources of lead in Krashnochelie nor in Lowozero, it is tempting to assign a substantial contribution from dietary sources in these communities, especially lead-contaminated wildlife meat. It is known from a questionnaire in parallel studies (Odland *et al.* 1996, 1997) that consumption of traditional foods is higher in communities with native inhabitants, presumably with a concomitant reduction in the use of canned foods. This applies especially to Krashnochelie. Follow-up studies are, of course, needed to confirm this hypothesis.

Increased body burden of lead in children is recognized to affect neuropsychological functions, as well as impairing auditory nerve conduction and hearing (Mushak *et al.* 1989; Schwartz &

Otto 1991; IPCS 1995; Rice & Silbergeld 1996). Consequently, since a significant number of the children in this study exceed the level of medical concern of 0.48 µmol/l, efforts to minimize lead intake are warranted (including education about lead sources). Furthermore, the occurrence of subclinical effects suggests that there may be no safe level of lead exposure for children (Todd *et al.* 1996). To reduce environmental contamination and human exposure, lead shot has been banned nationwide in some jurisdictions from use in water fowl hunting (USFWS 1988) and migratory bird harvesting (CWS and OFAH 1996).

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PAPER VI

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ORIGINAL ARTICLE

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Critical evaluation of medical, statistical, and occupational data sources in the Kola Peninsula of Russia pertinent to reproductive health studies

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Abstract *Background:* The feasibility study described herein was prompted by a report in 1992 of possible reproductive and developmental health concerns among female workers in a Russian nickel refinery. *Objective:* The primary goal was to ascertain whether medical, statistical, and occupational data bases could be accessed for information about the pregnancy histories, occupational histories, and life-style factors of the women affected. *Methods:* The project was facilitated by construction of a registry of all births in three towns with a nickel refinery and verification of its contents against patients' records obtained from hospital delivery and gynecology departments and community polyclinics. Municipal Registration Board, Regional Health Statistics Board, and nickel company records were also reviewed. *Results:* Reproductive/developmental outcome information and workplace histories were acceptable. Sample-size calculations indicated that a cohort or cross-sectional study would be amenable and suitable for the detection of an excess risk for spontaneous abortion with adequate statistical significance and power. Such investigations would need to be supplemented by workplace environmental/biological monitoring assessments for evaluation of exposure to occupational hazardous factors and a worker's questionnaire to obtain information about life-style factors. A case-control design is recommended for the study of congenital defects. *Conclusions:* A well-designed, comprehensive epidemiology study is technically feasible because of the availability of a favorable pool of study subjects, reproductive/developmental outcome data, information to control for major confounders, and suitable occupational records.

Key words Russia · Epidemiology · Nickel workers · Reproduction

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Introduction

In 1992, one of the authors (V.P.T.) presented a paper at the Fifth International Conference on Nickel Biochemistry, Toxicology, and Ecologic Issues that expressed concern about reproductive and developmental health effects in relation to occupational exposure of female workers employed in a Russian nickel refinery (Chashschin et al. 1994). Although exposures in this setting had been linked to increases in respiratory cancers (Doll 1990; International Agency for Research on Cancer 1990), no human evidence had previously been reported about reproductive health problems among female workers (Clarkson et al. 1985; International Program on Chemical Safety 1991). Since very few women have been employed in the nickel-producing industry in the Western world, studies of such effects have not been possible. The initial report by Chashschin et al. (1994) outlined evidence that warranted closer scrutiny and follow-up. In this article we describe an assessment of whether a full epidemiology study of Russian female nickel refinery workers is technically feasible. The main objective was to ascertain whether medical, statistical, and occupational data bases could be accessed for information about the pregnancy histories and occupational exposure of the female workers affected. The availability of relevant lifestyle factors was of special interest.

The concern

Human health perspective

Chashschin et al. (1994) have reported apparent increases in spontaneous abortions and structural malformations in newborn babies whose mothers have been employed in the nickel refinery at Monchegorsk. The pertinent data are reproduced in Tables 1 and 2. The authors conclude that abortion is more common among nickel-exposed workers than in a reference population and that there is a statistically significant increase in congenital defects in children born to these workers, more specifically, defects of the cardiovascular and musculoskeletal systems. Concerns about the reliability of these findings have been expressed, which may be itemized as follows (Nieboer et al., unpublished report):

1. The power of the Chashschin et al. (1994) study to detect a 2-fold increase in the rate of spontaneous abortions and related pregnancy complications appears adequate but is not satisfactory for the apparent 3-fold increase in structural malformations; this does not necessarily preclude a positive finding.
2. More information is needed about the selection of reference populations to assure the absence of selection bias.
3. Confounding factors need to be controlled for, such as smoking, age, socioeconomic status, ethnicity, or other occupational factors, alcohol and drug use during pregnancy, medical history, pregnancy complication, and paternal factors (e.g., age and occupation).
4. The characterization of exposure is inadequately documented.
5. Finally, the classification or terms describing some of the medical outcomes do not appear to conform to international conventions. Nevertheless, Nieboer et al. (unpublished report) conclude that since cardiovascular and musculoskeletal defects are possibly due to a common mechanism, their apparent enhancement together with the absence of previous epidemiology data on the reproductive effects of

Table 1 Pregnancy complications among Monchegorsk nickel electrorefinery workers (% of pregnancies recorded)[a]

Pathology[b]	ICD-9 code[b]	Nickel refinery workers (n = 290)[c]	Non-nickel controls (n = 386)[d]
Normal course of pregnancy	650	29.0	38.8
Threatened abortion	640	17.2*	7.6
Spontaneous abortion	634	15.9*	8.5
Gestational toxicosis (early)	642.4	12.9	13.5
Gestational toxicosis (late)	642.5	32.8	27.2
Pregnancy-induced hypertension	642.0–642.3	6.0	8.2
Anemia	648.2	11.2	12.9
Other complications	–	29.7	20.6

* $P < 0.05$
[a] Adapted from Chashschin et al. (1994)
[b] Based on medical records (Murmansk Region Health Statistics Board and hospital delivery department records), using the International Classification of Diseases, 9th revision. A questionnaire was also administered
[c] Selected from current employees in 1987; the total number of female workers employed in the nickel electrorefinery was 787
[d] Workers employed by the Kola Construction Company in Monchegorsk; the total number of females employed at the time of the survey was 602

Table 2 Adverse outcomes of pregnancies ending in delivery among Monchegorsk nickel electrorefinery workers (per 100 births)[a]

Pathology[b]	ICD-9 code[b]	Electrolysis operators (n = 232)[c]	Purification operators (n = 124)[c]	Total group (n = 356)[c,d]	Non-nickel controls (n = 342)[c,e]
Prematurity	644	8.6	4.8	7.3	4.1
Hypoxia	768	7.3	7.3	7.3	9.4
Hypertrophy	766	15.5	29.0	20.2	15.8
Stillborn babies	–	0.9	0.8	0.8	1.2
Structural malformations	740–759	16.4	17.7	16.9*	5.8

* $P \leq 0.05$; the relative risk for cardiovascular defects was 6.6 and that for musculoskeletal defects, 1.9
[a] Adapted from Chashschin et al. (1994)
[b] See footnote b, Table 1
[c] Number of mothers
[d] See footnote c, Table 1
[e] See footnote d, Table 1

nickel warrant further investigation of reproductive outcomes in this population.

The data listed in Table 3 constitute the official infant-mortality statistics kept by the Murmansk Region Health Statistics Board. These raw data also draw attention to the possibility of industry-related developmental effects. Clearly, the information reviewed generates genuine concern about reproductive and developmental health issues associated with occupational exposures (including nickel).

Animal studies

A range of effects have been reported in animal experiments (Sunderman et al. 1983; Environmental Protection Agency 1985; Sager et al. 1986; Coogan et al. 1989). Nickel salts are toxic to spermatozoa and embryos. Nickel is known to cross the placenta in rodents, with reported malformations at birth including ocular, skeletal, and neuronal effects; fetal hemorrhages and hematomas are also reported. The evidence for perinatal mortality appears to be the strongest (Smith et al. 1993). Experiments with nickel tetracarbonyl provide the clearest indication of teratogenicity manifesting as specific ocular effects (anophthalmia and microphthalmia; Sunderman et al. 1979, 1980; Nieboer et al. 1988). Chloride salts of Ni^{2+}, like those of Co^{2+}, Zn^{2+}, and Cd^{2+}, have been shown to be embryotoxic and teratogenic in the FETAX assay (frog embryo teratogenesis assay: *Xenopus*); observed defects included ocular malformations (Hauptman et al. 1993; Luo et al. 1993).

Objectives of the Kola feasibility study

The purpose of the Kola feasibility study was to investigate the possibility of conducting a well-designed epidemiology study of reproductive and developmental health effects among female nickel refinery workers. We therefore set out in the autumn of 1995 to collect information for assessment of the technical possibility of a detailed epidemiology study of fertility, spontaneous abortions, birth defects, and infant diseases. In this exercise the following were evaluated: the availability of medical histories (maternal and neonate), occupational histories (mother and father), work force demographics, life-style issues/parameters, and exposure data. The classification of diseases employed was also a focus.

Background about the Kola Peninsula

Industries in the Kola Peninsula are essentially mineral-based. In the corridor between Murmansk and Kandalaksia (see Fig. 1) the following industries occur: iron mining and refining (at Olenegorsk), uranium and thorium recovery (Revda), nickel mining and refining (Monchegorsk), apatite recovery (Apatity), nuclear power generation (Polarniy Zory), and aluminum refining (Kandalaksia). In addition, there are two nickel refineries in the northwest corner of the Kola Peninsula adjacent to the Russian-Norwegian border, namely, at Nickel and Zapolyarniy. At Zapolyarniy the operation consists of ore beneficiation, whereby the ore is milled and the mineral-rich component is separated by flotation and subsequently roasted. At Nikel the primary refining process is completed, whereby the ore concentrate is smelted and converted: the end product is referred to as nickel matte. At Monchegorsk, ore smelting and converting take place as well as the further refining of the matte into pure nickel (a process referred to as secondary refining). This is by far the largest plant. Although there are local ore supplies in the Kola Peninsula, sulfur-rich ore is shipped in from Norilsk in Siberia. It now constitutes the main source of ore. Ore roasting, smelting, and conversion release huge quantities of sulfur dioxide, which, together with the release of metals, has caused ecological devastation in the areas immediately adjacent to the aforementioned operations (the diameter of the pollution zone is 20–30 km; Norseth 1994). This environmental impact is similar to that seen in Sudbury, Ontario, Canada (Gunn 1995). By contrast, the areas of the Kola Peninsula east of the industrial corridor may be considered one of the most pristine and unspoiled areas in Russia and, indeed, in the world.

One feasibility study focused primarily on the Severonickel female work force at Monchegorsk, with special emphasis being placed on those working in the

Table 3 Infant mortality (below 1 year of age), deaths per 1,000 live births in the Kola Peninsula for the period 1971–1990[a]

Causes of death	ICD-9 code	Communities located in the vicinity of specific industries: Fertilizer mining	Nickel mining	Nickel refinery	Aluminum refinery	Regional expected
Selected causes in perinatal period	760–779	4.2*	3.7	4.6*	4.0	3.3
Birth defects	740–759	5.4**	3.3	4.1*	3.1	2.8
Respiratory diseases	460–519	2.0	3.2*	3.8*	4.1*	2.0
Other causes	–	6.1*	4.0	3.0	4.8	4.2
Total	–	17.7*	14.2*	15.5*	16.0*	12.3

* $P < 0.05$; ** $P < 0.02$

[a] Source: Murmansk Region Health Statistics Board

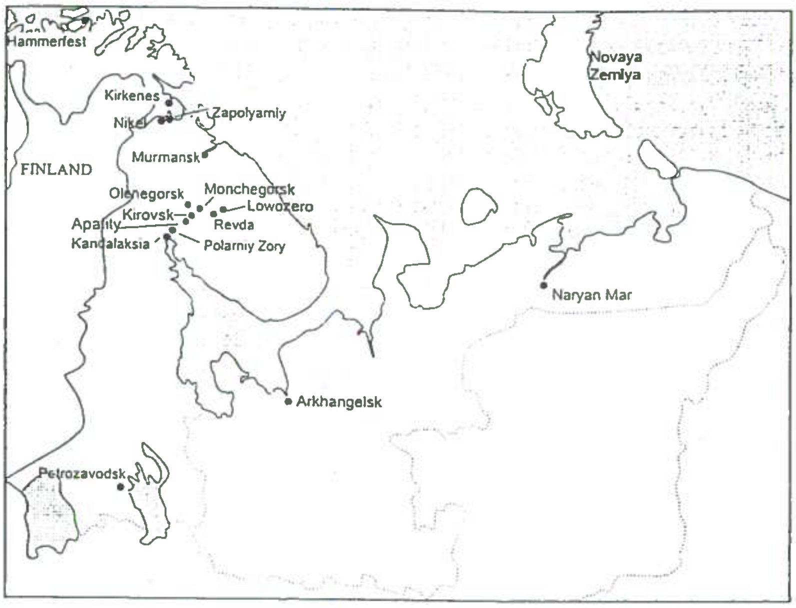

Fig. 1 Schematic map of the Russian Barents region (courtesy of Elin Hanssen, NILU, Tromsø, Norway)

electrorefining departments. Details for 1995 about the size of the work force are provided in Table 4.

Approach to the feasibility study

International research requires strong local, regional, and national connections, especially in the health community. One coauthor (V.P.T.) is the Director of the Kola Research Laboratory for Occupational Health (KRLOH) in Kirovsk. The KRLOH has basic clinical chemistry facilities, an epidemiology group, and a 40-bed hospital for the evaluation of workers with chronic occupational diseases. Its mandate is to monitor and assess occupational exposure and health in the various industries of the Kola Peninsula. The director reports to the Department of Sanitary and Epidemiologic Surveillance, Russian Federation, which is within the Ministry of Health.

It became obvious from informal discussions that the generation of a birth registry in the towns with nickel refineries, namely, Monchegorsk, Nikel, and Zapolyarniy, needed to be a primary objective. Such a registry would permit ready access to the relevant medical information, and its formal verification against patient journals would create an opportunity for the non-Russian members of the team to become knowledgeable about these matters. In the span of 2 years the KRLOH staff set up a computerized data base referred to as the Kola Birth Registry.

Table 4 Size of the Severonickel work force at Monchegorsk in 1995

Sector or department	Number of employees		
	Total	Females	Males
Main works[a]	5,011	1,151	3,860
Maintenance and services[b]	5,598	2,116	3,482
Nonindustrial sector[c]	2,226	2,110	116
Total, all sectors	12,835	5,377	7,458

[a] Including pyrometallurgical refining and hydrometallurgical refining, electrorefining, the nickel carbonyl plant, and sulfuric acid production (10 works)

[b] Including administrative personnel and other services

[c] Kindergartens, trade stores, farming, and other facilities located outside the nickel-refinery plant

Kola Birth Registry

In the calendar years 1996 and 1997 the Registry was constructed retrospectively for the towns of Nikel, Zapolyarniy, and Monchegorsk; it covered all births (total 4,752) for the period 1986–1993. The registry project was first begun in Nikel and Zapolyarniy. During 1998 the number of entries were nearly doubled by inclusion of the years 1981–1985 for Monchegorsk. On command the Registry provides individual or summary information about specific particulars/outcomes of the mother or her newborn baby, including maternal employment/occupation details, pregnancy number and outcomes, and the health status of the neonate (see Table 5). The sources of information were the hospital delivery department journals and the Municipal Regis-

Table 5 Table of contents of the Kola Birth Registry[a]

* Code number	* Date of birth
* Gender of neonate	* Parity
* Gestational age	* Weight of baby
* Height of baby	* Head circumference
* Chest size	* APGAR score
* Delivery complications (660–669)	* Pathology baby (yes/no)
* Age of mother	* Occupation (mother)[b]
* Place of employment (mother)[b]	* Education (mother)
* Age (father)	* Occupation (father)[b]
* Place of employment (father)[b]	* Education (father)
* Number of pregnancies	* Number of deliveries
* Number of abortions (medical/spontaneous)	* Number of preterm deliveries
* Health status of newborn	* Complications (newborn)
* Prematurity[c] (644)	* Hypotrophy[c] (764)
* Very large size (766)	* Hematoma[d] (767.0)
* Anemia (mother) (648.2)	* Thoracic abnormalities (cardiac, 745–747; diaphragmatic, 756.6)
* Respiratory distress (770)	* Malformations (740–759; yes/no)
* Anencephaly[d] (740)	* Fracture (767.1–767.7)
* Infections (mother) (647)	Hypoxia[c]
* Other pregnancy complications (640–643, 645–646)	* Other selected perinatal causes of death (760–779)

[a] ICD-9 codes are given in parentheses where applicable
[b] The following workplace categories are used: mining, plant/department, office work, education, health professional, retail, food services, construction, other
[c] Three grades of severity are used
[d] Two grades of severity are used

tration Board (see below), supplemented by hospital gynecology journals. Hospitals are required to archive 25 years from the date of birth structured forms detailing each birth and neonatal history. Since 1973 the Regional Health Administration of Murmansk County and the Federal Ministry of Internal Affairs have exercised strict supervision to ensure the accurate and complete registry of all deliveries. In 1993 the federal authority was consolidated under the Federal Law of Archives.

Approach to the verification of the Kola Birth Registry

For 54 females and their newborns the data recorded in the Kola Birth Registry (up to 39 items for each pair, see Table 5) were checked in a blind fashion against the personal delivery department journals. To keep personal information confidential, codes instead of names were used to follow up information on randomly selected mother/neonate pairs in the three communities. In Nikel and Zapolyarniy, one of us (E.N.) asked the questions for which answers were sought (i.e., according to the table of contents of the Registry; see Table 5), and he also acted as the recorder. Another member of the team (J.Ø.O.), together with a Russian colleague (Deputy Chief of the Nikel and Zapolyarniy hospitals), extracted the appropriate information from the journals. The protocol was similar in Monchegorsk except that one of us (V.P.T.), together with a colleague from the KRLOH, extracted the required information from the journals. In addition to verifying personal parameters about mothers and their babies, the verification exercise afforded detailed insights into the quality of record keeping, the classification of diseases employed, including, birth defects, and the medical terminology used. This permitted us to become familiar with patients' details on reproductive and developmental health available through the hospital delivery department journals (Table 6) and the hospital gynecology journals (Table 7). It also prompted us to visit the onsite medical department at Severonickel.

Overview of the medical documentation

Each adult male has a medical journal that is kept in the Adult Polyclinic. For females there are three data sources, namely, the Adult Polyclinic for the general medical history, the Hospital Gynecological Polyclinic for the reproductive issues, and a more specific reproductive history on the admission to the Hospital Delivery Department. The personal, reproductive, or reproductive/neonatal information available in the delivery and gynecology journals are summarized in Tables 6 and 7. Deliveries with medical complications are handled locally most of the time; if required, medical experts are brought in to consult with the attending physicians and midwives. Consultations with appropriate experts in Murmansk occur frequently. Records are available on women who are transported to Murmansk.

Ultrasound screening procedures for all pregnant women were established at the Gynecological Polyclinic in Monchegorsk in 1994, but not in Nikel and Zapolyarniy. Since that time, all pregnant women have received an ultrasound screening of the fetus during week 19 of pregnancy at the Monchegorsk hospital, except for the 5,400 women employed by the Severonickel Company (the Kombinat; see Table 4). They

Table 6 Personal and health information recorded in the hospital delivery department journals

* Date of birth	* Mother's name
* Mother's age	* Gender
* Parity (number of child)	* Gestational age (weeks)
* Weight of baby (g)	* Length of baby (cm)
* Head circumference (cm)	* Chest size (cm)
* APGAR score	* Delivery complications
* Mother's health status and pathology	* Occupation (mother)
* Place of employment (mother)	* Father: name, age, occupation, health status
* Number of pregnancies	* Number of deliveries
* Number of spontaneous abortions	* Number of induced abortions
* Number of induced abortions	* Number of preterm deliveries
* Birth weight of previous children	
* Health status of newborn and diagnosis	

Table 7 Personal and health information recorded in the hospital gynecology journals

* Name	* Birthday
* Marital status	* Number of marriages
* Nationality	* Education
* Address	* Condition of flat
* Place of work	* Work conditions
* Husband's name	* Husband's job (company, department)
* Information of previous pregnancies	* Contraceptive use
* Familial diseases	* Personal medical history
* Health information about husband	* Special treatment details/special consultations
* Social life assessments	

obtain equivalent prenatal care through the Severonickel Polyclinic, which is supervised by the chief physician of the local Adult Polyclinic. There are plans to extend screening of the pregnant population to all of Murmansk County, hopefully in connection with a few special centers such as Monchegorsk. All abortions, including medical abortions, were investigated macroscopically and histologically (total fetoplacental unit) until 3 years ago, when this was stopped for economic reasons. The corresponding records are available. All abortions (spontaneous or induced) are registered in the women's journal of the Gynecological Polyclinic. All stillbirths and induced abortions are reported to the Municipal Registration Board. There is a special perinatal committee in hospitals that is responsible for investigation of stillbirths and medical reasons for recommending abortions (including fetal maldevelopment). All journals of patients with special problems, such as alcoholism, hepatitis, and other severe infections, among others are marked with a red line across the journal title page.

All diagnose are registered using the ICD-9 classification system, with small national adaptations. This means that the normal obstetric and perinatal diagnoses are comparable with the international standard. However, slight differences do exist in nomenclature and interpretation. For example, pre-eclampsia, gestosis, toxemia, nephropathy, and gestational anemia can be related to specific ICD-9 codes for pre-eclampsia. The ICD-10 classification system is scheduled to come into effect in 1999.

The Monchegorsk Children's Polyclinic illustrates the personal and medical information available for children. The Delivery Department informs the Children's Polyclinic when mother and child are discharged. Shortly thereafter, a home visit is made by the district pediatrician and nurse (there are 21 such districts in Monchegorsk) and a report is filed. If all is well, the nurse drops in routinely once a week during the 1st month; on day 21 the pediatrician visits. If there is a health concern, the nurse makes two visits per week and the pediatrician, one. At the age of 1 month the child brought in for a full checkup and all the particulars are recorded on Form 112. Subsequently, there is one visit a year to the polyclinic. Neuropathological, ear-throat-nose, and ophthalmological assessments are emphasized. The child's journal is stored for 1–2 years after the 1st year; if everything is normal, it is sent home when the child attends kindergarten. A summary record, specifically, Form 30U, is kept by the Children's Polyclinic for all children; it is transferred to the Adult Polyclinic when the child is 15 years old. When there are health problems the complete journal is kept by the district pediatrician. In this case, when the child is 15 years of age a copy of the journal is passed on to the Adult Polyclinic. All vaccination records are coordinated through the Children's Polyclinic, even though the vaccination program is carried out through kindergarten and school. When the child is 15 years of age the vaccination record, Form 63, is also sent to the Adult Polyclinic. Since 1995, a computer data base has existed for recording of all home and polyclinic visits by children.

Statistical data bases

Records of birth, marriage death (including cause), and last occupation are kept by the Municipal Registration Board. Population-based statistical information about disease patterns are compiled by the Murmansk Region Health Statistics Board. Detailed computerized files of work and medical/reproductive histories are kept at the KRLOH on the Severonickel work force. Ministry of Health regulations permit unlimited, although confidential, access by KRLOH physicians to archived and current health information and personal data in municipal and company records. Epidemiological assessments are also conducted by KRLOH staff to identify special risks or to compile disease patterns (e.g., of cancer or cardiovascular disease).

Company records

Employees are listed in alphabetical order and the records go back to the 1950s. Prior to the passage of the Federal Law of Archives in July 1993, company records were kept for 50 years; archiving for 75 years is the current requirement. Structured personal charts for each worker have been and are mandated by law to record 22 items of information, including the date and place of birth, the date of first employment and duration of employment, education and training, previous employment, department, major jobs, major sick leaves, and the results of any medical examinations/treatment at the company's onsite medical department (polyclinic). Company medical records are coordinated with those of the local adult and gynecological polyclinics. Personal worker charts for defunct companies are transferred to a municipal archive.

Prior to the current unstable economic period, only 6% of the work force retired in the Kola Peninsula and, thus, follow-up until death is difficult. Consequently, cohorts defined for epidemiology studies can include only men aged 20–55 years and women aged 20–50 years. Current retirement practices are not established. The upper end of these ranges correspond to the official retirement age. All sick leaves are recorded and supported by medical examination. All workers received an annual checkup or a more complete medical examination if warranted by the potential occupational risk associated with their job. Females constitute about 30% of the employees who work in areas with a potential for exposure to nickel (see Table 8).

Interpretation and critical evaluation of the information sources

General comments about the Russian health system

Generally speaking, Russian medical-care delivery differs from Western practices mostly in preventive/prophylactic practices. Pertinent techniques not usually employed in Western medicine may include acupuncture, electrolysis, electric field stimulation, pressure message, water therapy, and intravenous laser treatment, among others. However, these practices do not impact on reproductive or developmental health care. Postpartum stays in hospitals by mothers last at least 1 week. The clinical chemistry support is generally weak.

Assessment of medical records

Record archives in hospitals and polyclinics appear to be well organized, since the journals requested by us were produced on short notice. Inventories are not computerized an all medical records must be kept for 25 years. Record keeping might be designated as good, with some tendency to provide more details than are warranted. The completeness of official birth and neonatal history forms was checked by KRLOH staff for each Birth Registry entry. On the basis of this check it may be concluded that very few items/boxes on the official patient documents (forms) have been left unanswered. Information about male partners other than the name tend not to be answered in the delivery and gynecology journals. Presumably, if these were needed in a follow-up, they could be obtained from the Adult Polyclinic. Abortions (spontaneous or induced) are registered in the gynecology journal. The availability up to early 1995 of the pathology reports on all aborted fetuses (spontaneous or induced) further strengthens future investigations about birth defects.

Official statistical records

An inspection of the data in Tables 1–3 indicates the type of group-based adverse pregnancy outcome information that is available for nickel workers and reference populations through the Murmansk Region Health Statistics Board. By order of the Ministry of Health, every medical unit within a region must annually report to this board, for example, the number of births and deaths, number and type of delivery complications and pregnancy outcomes, and new cases of ICD-9 coded diseases. Numbers of births and deaths can be cross-checked with those in the Municipal Registration Board data base. These official sources constitute a starting point for any epidemiology work, and the information available can be readily supplemented with additional details derived from medical records kept in hospitals (e.g., delivery department) and polyclinics (children, adult, gynecological).

Assessment of the Kola Birth Registry

In the Monchegorsk component of the Registry data base the percentage of incorrect items was very low (< 1%), attesting to its reliability. By contrast, the detailed verification of the Nikel and Zapolyarniy entries was abandoned. The reason for this was the identification of significant errors in record identification and item recording. Although some recording errors during the site verification might have occurred, this is unlikely, as the process was carried out under the scrutiny of three individuals. A more satisfactory explanation is that the Kola Birth Registry was initiated in Nikel and Zapolyarniy and, as a consequence, the data collection/transfer protocols suffered from staff inexperience.

Table 8 Current number of workers employed in the nickel-refining industry by cities in Russia

Employee category		Processing of sulfidic ores		Processing of oxidic ores (Pyrometallurgy)			
		Monchegorsk (Severonickel)	Nikel + Zapolyarniy (Pechenga Nickel)	Norilsk (Norilski Nickel)	Orsk	Verkhniy Ufaley	Revda
Total work force	153,327	12,835	10,395	115,812	7,734	3,590	1,046
Females	63,006	5,377	3,699	48,645	3,000	1,170	316
Workers highly exposed to industrial hazards[a]:							
Total	51,177	7,486	4,618	31,149	5,444	2,480	–
Females	14,733	2,662	646	9,045	1,712	668	–

[a] Exposures reported to exceed the Russian occupational limits

The reviewers made a number of suggestions for improvement such as the recording of sequential APGAR scores (1 and 5 min) rather than only a single value (usually at 1 min). A protocol for independent verification for any new data entries was also recommended and adopted. Since 1997, KRLOH staff have double-checked and edited all previous entries and have proceeded to add new entries as well as new fields pertaining to the development of disease or defects in children up to the age of 15 years using children's journals or the summary childhood records kept in adult polyclinics.

It is clear that the Kola Birth Registry does not contain adequate information about the occupational histories of the female workers. Information is limited to the place of employment and the job title at the time of birth. It also does not provide details about life-style factors such as smoking habits and alcohol consumption. Information about the father of the child is often missing, including his name; if particulars are provided, these are confined to a statement about his general health, place of employment, and job title.

Work-force demographics and company records

Company records are adequate for establishment of the major departments in which workers have spent significant periods of time (≥1 year). Detailed personal exposure data are not measured and are thus not available. However, area ambient air concentrations of dust and nickel have been part of the reporting structure within the Federal Department of Sanitary and Epidemiologic Surveillance. From the data compiled in Table 8 it is evident that about 2,660 females and 7,490 males are potentially exposed to industrial hazards at the Monchegorsk Severonickel complex. By comparison, there are fewer nickel-exposed individuals (especially females) at Pechenga Nickel, which has refineries at Nikel and Zapolyarniy, whereas the numbers at Norilsk are considerably larger.

KRLOH data bases

Through contractual arrangements, KRLOH provides occupational health services to Severonickel. Since 1980, staff of the KRLOH have prepared occupational histories for the Kola Peninsula nickel workers on the basis of the structured personal charts mentioned above and the medical histories. This computerized data base can readily be combined with the appropriate statistical information available through the Monchegorsk Municipal Registration Board and the Murmansk Region Health Statistics Board. Raw and standardized statistical information about reproductive and developmental health, morbidity rates, and mortality rates from major causes (with cancer being an outcome of major occupational importance) is maintained and continually updated. Furthermore, cross-sectional work-related health studies have been completed by KRLOH staff. Some of these findings have been published (Chashschin et al. 1994; Norseth 1994).

Conclusions

General observations

This study indicates that the Kola Birth Registry provides medical documentation suitable for epidemiology research. If required, this type of information can be supplemented by consultation of the original patient journals. By contrast, the Registry does not adequately document socioeconomic and life-style factors (e.g., family history of inherited diseases, family income, contraceptive use, breast-feeding practices, nutrition particulars, and alcohol and tobacco use). This type of information needs to be accessed through a questionnaire. Our experience with an interview format was satisfactory (Nieboer et al., unpublished report); the interviewers were physicians. Clarification about the working environment beyond the information available through company records may also be obtained in this manner, such as on the presence of recognized hazards (e.g., vibration, other physical agents) or the physical demands of the job.

A perusal of the sample-size calculations summarized in Table 9 indicates that some type of cohort or cross-sectional study would be suitable for the detection of an excess risk for spontaneous abortion. Assuming a background rate of 8% (see Table 1) and a risk ratio

Table 9 Sample-size calculations: spontaneous abortions and major birth defects[a] [cohort/cross-sectional studies; $\alpha = 0.05$, $\beta = 0.20$]

Relative risk (RR)	Spontaneous abortions (background rate 8%)[b]		Major birth defects (background rate 1%)[c]	
	Number of pregnancies[d]		Number of births[d]	
	Exposed	Nonexposed	Exposed	Nonexposed
1.3	2,358	2,358	20,488	20,488
1.5	931	931	8,145	8,145
2 0	282	282	2,514	2,514
3.0	93	93	865	865

[a] Calculated using Epi Info 6, Version 6.04a, July 1996 (WHO, Geneva)
[b] See Table 1
[c] Taken from 1995 Annual Report, Medical Birth Registry of Norway
[d] Exposed/nonexposed ratio of 1

(RR) of 1.5, about 1,000 pregnancies (excluding induced abortions) need to occur among both exposed and nonexposed subjects. From our feasibility study (Nieboer et al., unpublished report) it is evident that females have about two pregnancies (excluding induced abortions) per lifetime, of which one occurs during employment in the nickel refinery. Consequently, the lifetime pregnancy histories of about 1,000 each of exposed female workers and referents need to be included in an epidemiology assessment to detect a relative risk (RR) of 1.5. Of course, this requirement is reduced to 200–400 for an RR of 2.0 (see Table 9). Since in the Monchegorsk nickel refinery about 1,151 female workers are currently employed in areas associated with significant nickel exposure, 1,511 (2,662–1,151) are potentially exposed, and 2,110 are nonexposed (see Tables 4, 8), one may conclude that a cohort study of the lifetime pregnancy outcome for the period 1970–2000 or of current workers would have adequate statistical significance and power to detect an excess risk for spontaneous abortion.

The study of major birth defects requires a different epidemiology strategy. A cohort or cross-sectional design would require a female cohort or current work force somewhat larger than that available in Monchegorsk (see Table 9). However, as shown in Table 10, a case-control study appears to have acceptable statistical significance and power, as around 100 cases are required to detect risks corresponding to odds ratios (OR) of 2.0–2.5, the values suggested by the raw data in Table 2. Current efforts to expand the Kola Birth Registry should improve the ability to detect a significant result, if one exists.

Since personal exposure data are not available, environmental and biological monitoring assessments need to be done. A comprehensive exposure assessment of the nickel workers employed in two departments of the Severonickel refinery at Monchegorsk has shown that they are heavily exposed, primarily to nickel (Thomassen et al. 1999). Such data may be considered to reflect past exposures as well, since few operational changes have occurred in recent times.

Table 10 Sample-size calculations: major birth defects[a] [case-control study; $\alpha = 0.05$, $\beta = 0.20$]

Odds ratio (OR)	10% Nickel workers[b] Number of births[c]		20% Nickel workers[b] Number of births[c]	
	Cases	Controls	Cases	Controls
1.5	703	1,406	415	830
	576	2,304	342	1,368
2.0	223	446	137	274
	180	720	111	444
2.5	121	242	76	152
	97	388	62	248
3.0	81	162	53	106
	64	256	42	168

[a] Calculated using Epi Info 6, Version 6.04a, July 1996 (WHO, Geneva)
[b] Percentage of mothers who are employed in the nickel refinery
[c] The first entry for each OR value corresponds to a controls/cases ratio of 2 and the second entry corresponds to a ratio of 4

As a practical result of our work, the Federal Government of Russia is considering extending a simplified version of the Kola Birth Registry to all counties of the federation. The staff of KRLOH act as principal advisers to the Federal Health Department, with the other authors constituting an expert advisory group. We have also initiated a cohort study of lifetime pregnancy outcomes for the period January 1, 1970, to January 1, 2000, as well as a case-control study of birth defects within the Birth Registry described.

Personal observations

In a recent commentary, Little and colleagues (1997) indicated that differences in disease classification presented an obstacle to epidemiology research in countries that had formerly been a part of the Soviet Union. From the gynecological perspective, such differences were readily resolved in the present study through discussions that focused on the application of the ICD-9 classification, which was available in the Russian language. Language barriers also did not seem to present a serious obstacle. In the extended team (i.e., the principal investigators and their support groups) there were individuals who spoke both English and Russian. The increased facility with the English language by our Russian colleagues during the project was impressive. Working together clearly helped in this development. Finally, it is our experience that trust and acceptance were the most important ingredients in this cooperative international project.

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