



From women's health to gender medicine

An anthology



SWEDISH COUNCIL FOR WORKING LIFE
AND SOCIAL RESEARCH

From women's health to gender medicine

An anthology

The Swedish Council for Working Life and Social Research initiates and funds basic and applied research with a view to improving our knowledge about working life, public health and welfare.

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Preface

FAS provides funding for research into working life, public health and welfare. While the Ministry of Health and Social Affairs is the primary principal, FAS also receives assignments from other ministries. In 2007 the Ministry of Integration and Gender Equality commissioned FAS to implement an investment in women's health, the Ministry having set aside SEK 30 million annually for three years for this purpose. FAS decided to announce the funds for projects, networks and guest researchers in this area. The research programme generated extensive interest and 140 applications were received. Most of the funding, SEK 86 million, went to research projects, 17 being initiated in 2008. Grants were later provided to six networks and one guest researcher. Overall the approved projects represent a multitude of issues with central significance for women's health and demonstrate an interesting range of theoretical premises and methodological approaches.

FAS made an early decision to highlight the investment by issuing a publication that would give some project funding recipients an opportunity to present their projects. We believed the urgency of the research area made it desirable to mark the investment at an early stage. Consequently, there are as yet no concrete research

findings of significance to report from the projects; instead, the book provides a broad background sketch of the area. FAS has not seen it as its task to define the research field of women's health, but has chosen primarily to grant funding for projects of a high scientific calibre and relevance within FAS's sphere of activity.

The intention was both to increase knowledge within the area and to build research environments that can continue to develop after completion of the projects. Against this background, the employment of younger researchers and doctoral students within the project framework was also emphasised. Interdisciplinary approaches were welcomed, as was collaboration between different research environments. Another feature of the programme was the possibility of drawing international expertise into the research and promoting networking and cooperation. At the end of the programme period, there will follow a concerted evaluation of the programme investment which will include scientific publications, the establishing or consolidation of research environments, and research communication and social dialogue.

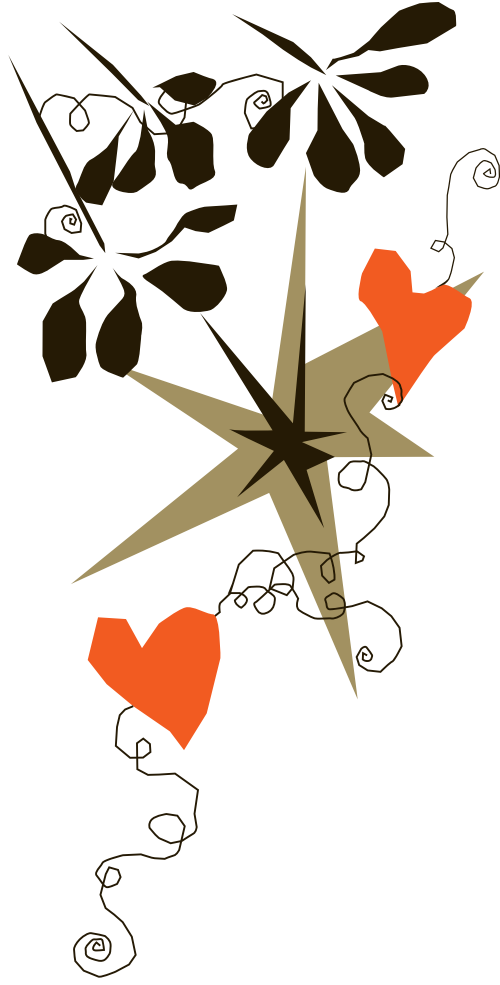
While this book does not answer all the essential questions regarding women's health, it does demonstrate the importance of continued, in-depth research in this field.

Finally FAS wishes to thank science journalist Sara Bergqvist Månsson, who has edited the book and helped make it accessible to a broader audience of readers.

Stockholm, May 2010

Erland Hjelmquist

Professor and Secretary General of FAS



Introduction

Karin Schenck-Gustafsson, Professor of Cardiology, Director and founder of the Center for Gender Medicine, Karolinska Institutet

The November 2009 ‘Open Comparisons’ from the National Board of Health and Welfare reports that women still do not receive optimal care – a highly surprising statement after all the efforts over the years to address this long-established fact.

Women’s expected rise in life expectancy has slowed to a rate which is lower than at any time in the last fifty years. In Sweden, mean survival was formerly ten years longer for women than for men, but the gender gap has diminished and mean survival is now about 81 years for women and 78 years for men. Survival is thus diminishing for women while it is increasing for men.

The cause of this Swedish phenomenon is unclear. Could it be due to the telomeres, which diminish in length in women as a result of stress and hence lose their ability to prolong life? Could the reason be that Swedish women have stopped taking oestrogen when they reach the menopause and thus receive no cardiovascular protection? Or is it that postmenopausal blood lipid and blood pressure levels are rising more than before because of increasing stress? Or that more women smoke than men?

We do not know the answers yet, but research into women’s health is continually adding new pieces to the puzzle about illness and health in a gender perspective.

What is gender medicine?

Traditionally, women's health has been seen as comprising illnesses linked to the reproductive organs. This perception of women's health has been called 'the bikini view'. Some hospitals still maintain special departments for women's health – the division or department of women's (and children's) health – but these are invariably linked exclusively to obstetrics and gynaecology. It does not occur to people that diseases other than those connected to the reproductive system may also be true diseases of women, i.e. they affect women far more than men. Examples include rheumatoid diseases, multiple sclerosis, whiplash injuries, pulmonary hypertension, gallstones, thyroid conditions, depression, anxiety conditions, eating disorders, fibromyalgia, chronic fatigue syndrome and osteoporosis. How sex hormones influence various widespread diseases is still relatively unknown.

Cardiovascular disease – not cancer, as many believe – is still the most common cause of death in women. The incidence of cardiovascular disease increases sharply after the menopause along with increased incidences of diabetes, systolic hypertension, metabolic syndrome and blood lipid disorders. Worldwide, cardiovascular disease is the leading cause of death in both genders – ahead of deaths from HIV/AIDS, malaria and TB combined. Of all deaths among women in Europe and Sweden, 23 per cent are caused by myocardial infarct and 18 per cent by stroke. 21 per cent of men die of myocardial infarct and 11 per cent of stroke. In Sweden, 50 women die each day of cardiovascular disease. While deaths from myocardial infarct are diminishing in both men and women in Sweden, the trend is not as pronounced in women. In Eastern Europe and the USA, deaths from cardiovascular disease are increasing among women.

Cardiovascular disease has become one of the most high-profile areas in terms of a gender perspective within medicine. Some very specifically female aspects of cardiovascular disease have been identified, for instance that risk factors may have a different significance or different prevalence in women.

There are specific hormone-related risk factors for cardiovascular disease in women, such as early menopause. Women develop myocardial infarct and stroke 10 years later than men and therefore enjoy some form of protection against cardiovascular disease at a younger age. For this reason early menopause, i.e. before age 45, is a risk factor for future cardiovascular disease.

Smoking reduces endogenous oestrogen levels, thus causing women who smoke to enter the menopause too early. Diabetes mellitus removes the cardiovascular protection, and so diabetic women suffer myocardial infarcts at the same age as men.

Polycystic ovarian syndrome (metabolic syndrome in women), with irregular menstruation, sex hormone imbalance, ovarian cysts, slightly elevated blood lipids and blood pressure and insulin resistance, also increases the risk of future cardiovascular disease.

Pre-eclampsia, hypertension and gestational diabetes, and complications of delivery can also increase the long-term risk, and there is much discussion nowadays about so-called fetal programming.

These special risk factors represent fairly new knowledge, and researchers in Britain and Finland in particular have taken an interest and have recently published papers in this area.

How the body's physiological systems are affected by myocardial infarct may vary between women and men. Women can have a myocardial infarct by standard diagnostic criteria but with so-called normal coronary vessels, and plaque erosion is more common than plaque rupture as the cause of myocardial infarct in women. During a myocardial infarct, women are more likely than men to experience various other symptoms such as dyspnoea, fatigue or influenza-type complaints along with their chest pain.

The leading cause of heart failure in men is myocardial infarct; in women it is hypertension. Men more often have systolic dysfunction (impaired cardiac pumping capacity) while women have what is known as diastolic heart failure (difficulty in filling the heart with blood). Because most studies are now carried out on systolic

heart failure, it is still unclear how women's diastolic heart failure really should be treated.

Diagnostic criteria sometimes differ between women and men and have not always been appropriate for women; nor is the treatment, treatment response or prognosis in cardiovascular disease always the same in women as it is in men.

The same applies within several other disease areas. Some claim that psychiatric disorders, substance abuse and pain are among the most gender-blind areas. These conditions affect men and women differently and have different causes.

Chronic pain is much more common in women. This applies for instance to fibromyalgia, stress headache and migraine. Using modern methods of investigation such as PET scans, American researchers have shown that cerebral flow patterns look different in male and female patients during various pain experiences and after administration of pain relievers. There is a gender difference in the activation of serotonin receptors in the brain during depression, and women have more serotonin receptors than men. Women respond better to SSRIs in depression. We know that sex hormones influence the brain, but how and to what extent has yet to be fully explored. It remains unclear why more women than men are affected by depression and other psychiatric conditions such as anxiety syndrome and eating disorders. Men are more prone to alcoholism.

Many researchers are now investigating the link between sex hormones and illness. As an example, in 2006 the US Mayo Clinic announced the discovery of a possible association between variants of three genes that regulate oestrogen production and the occurrence of Parkinson's disease in women. At UCLA in California, a male gene, SRY, has been identified which may have significance for Parkinson's disease in men.

When the uterus explained it all

Already in the 19th century, women's health focused only on the reproductive organs, the uterus and ovaries being regarded as the controlling organs. For instance, it was believed that tuberculosis was caused by irregular menstruation and that mental illness was linked to problems with the uterus (the Greek word for uterus is hystera). One way to cure these poor women in the 19th century was therefore to remove their uterus – hysterectomy. In Paris, the neurologist Charcot liked to exhibit his hysterical female patients to his male colleagues and medical students, as a famous painting shows.

Medical research in the 19th and 20th centuries was traditionally carried out by men who were researchers and doctors with primarily male experimental subjects and patients. They used themselves as the prototype ('70 kg white male'). But when they needed to fine-tune their surgical techniques, they often used female slaves.

During the second half of the 20th century, medical science resisted acknowledging the significance of gender, for instance in drugs trials. It was thought that the trials could be carried out in men and the results then extrapolated to women. One important reason for this was that researchers wanted to avoid fetal injuries, and did not dare expose younger women to trials of new medications. The experiments on pregnant women in Second World War were fresh in people's memories, and there was also the thalidomide catastrophe in the 1950s. Consequently, all early drugs trials were conducted in men, primarily firemen and medical students.

What you miss by excluding women from drugs trials is that women sometimes need different dosages – usually lower – and may experience more and different types of adverse effects as well as more drug interactions, e.g. because they are on hormone therapy. Also of significance are gender differences in the prevalence, causes, diagnosis, response to treatment, and disease prognosis that may alter the response to drug treatment.

Modern research

In the 1970s and 1980s, the US Food and Drug Administration recommended that fertile women should not be excluded from drugs trials and that an appropriate number of women should be included, corresponding to the prevalence of the disease. This applied particularly to cardiovascular disease. In the 1980s, as the Women's Health Movement gained momentum in the US, the focus broadened to include not only cardiovascular disease but also breast cancer. Progress in the treatment of breast cancer was also considered to be poor.

The breakthrough came in 1993 with the Revitalization Act, which required that women must be included in clinical studies in sufficient numbers to allow evaluation of the effects of the treatment given. In 1994 the US Institute of Medicine noted that two-thirds of diseases affecting both genders had been studied only in men.

An increase in studies demonstrating gender differences was then seen for a number of years, but a review of studies funded by the National Institutes of Health (the most powerful research council in the world) published in JAMA, the Journal of the American Medical Association, in 2001 found that cardiovascular studies included only 38 per cent women. This was deemed too little considering the prevalence of the diseases. A recent follow-up published in October 2008 in the American Journal of Cardiology showed that, while too few women were included in cardiovascular studies between 1996 and 1998, the number then remained adequate until 2004 when again a backlash occurred, with too few women being included up until the review ended in 2006.

In the framework of the Euro Heart Health Project Work Package 6, the World Heart Network and the European Society of Cardiology recently published a meta-analysis of all cardiovascular studies conducted between 2006 and 2009. The analysis included a total of 62 cardiovascular studies with 380,891 participants, 127,716 of whom were women, i.e. 33.5 per cent. The mean age was 66 years and the mean follow-up period 2.7 years. The proportion

of women included ranged from 15 to 60 per cent, but only half the studies had analysed their results with respect to gender.

In the area of cancer, the journal *Cancer* published in August 2009 a meta-analysis of 661 clinical studies of cancer drugs. The analysis included about one million patients. The studies analysed were concerned not with gender-specific forms of cancer, but with conditions such as lung cancer, oral cancer, brain tumours, colon cancer and lymphoma. The researchers recorded the respective proportions of male and female study participants. The proportion was determined both for all studies combined, and for each study separately. In both cases, the proportion of women was found to be lower than expected. Looking at all the studies, 38.8 per cent of participants were women. For all six types of cancer reviewed, the proportion of female participants in the studies was lower than the proportion of women affected by the respective form of cancer. Trials partly funded by government grants were slightly better than those that were privately funded.

In 2001 the US International Institute of Medicine published a report which confirmed the importance of gender differences in the prevalence and severity of a large number of illnesses including especially common forms of cancer, autoimmune diseases, central nervous system disorders and cardiovascular disease.

Since then, specific centres for gender medicine research have been established in Europe. The first was the Center for Gender Medicine at the Karolinska Institute. In the USA, the Organization for Studies of Sex Differences was established in parallel with the European International Society of Gender Medicine, the two organisations collaborating. Every year one meeting is arranged in USA and one in Europe at which part of the programme is shared. In Europe, congresses have taken place in Stockholm, Berlin and Vienna.

Six European universities are participating in an Erasmus project within the EU which offers a Master's programme in Gender

Medicine. One of these partners is the Center for Gender Medicine at the Karolinska Institute.

The Stockholm centre has provided research funding to some 40 research groups, about ten doctoral projects and numerous research and teaching positions within gender medicine. There has been a special focus on cardiovascular disease, the central nervous system (CNS), sex hormone research, endocrinology including kidney diseases, and inflammatory diseases.

This book

In Sweden, the Government has recently invested large amounts of money in women's research, part of this funding being allocated to FAS. In the present publication, some of the researchers who have received research grants from FAS write about their research. Their areas include prevention of cardiovascular disease, living with cancer, medications in older women, gender differences in the treatment of refugees, and various CNS-related studies.

This book truly highlights the need for research of this kind, and how important it is that it should be allowed to continue and new resources be invested.

Expect some exciting reading!

Stockholm, May 2010
Karin Schenck-Gustafsson





Osteoporosis a female problem – on brittle bones, fractures and women

Kristina Åkesson, Professor, Department of Orthopaedics, Malmö, Skåne University Hospital and the Department of Clinical Sciences, Malmö, Lund University

Osteoporosis occurs primarily in older women – but why? What genes and lifestyle factors control bone quality in the course of a woman's life? This is a question being investigated by Professor Kristina Åkesson and her co-workers. One of their findings is that women who smoke have poorer bone quality as early as the age of 25.

Osteoporosis, or brittle bones, is a condition in which the resilience of the skeleton diminishes. Lowered resilience increases the risk of fractures (broken bones) even after minimal trauma. Every year about 70,000 osteoporosis-related fractures occur in Sweden. Three-quarters of those affected are women, most of them over 70 years of age. Breaking a bone reduces your quality of life for a shorter or longer period because of the loss of function. You cannot walk or grasp things, you may not be able to cope on your own, and the pain makes it hard to be active. Knowledge about osteoporosis and osteoporosis-related fractures has grown enormously in the last 20 years, from the discovery of the

rising incidence of such fractures to the availability of several drugs that can reduce the risk of fractures by strengthening the skeleton.

What is osteoporosis?

Osteoporosis is defined as a condition where the mineral content and density of the bone diminish and its structure changes, making it less tough and more prone to injury when exposed to stress. The skeleton becomes more brittle and the bones break more easily if you fall. This makes osteoporosis essentially a matter of resilience, and the condition as such produces no symptoms or complaints unless it results in a fracture of some kind. Osteoporosis is therefore usually called a ‘silent’ condition until a fracture occurs.

Osteoporosis is caused by an imbalance in the normal bone metabolism. Bone tissue contains cells that build up (osteoblasts) and cells that break down (osteoclasts) bone. Both cell types are needed for the continuous repair of minor injuries and to maintain the tissue in optimal condition. One more cell type, the osteocyte, senses when an injury has occurred and acts as a signal transmitter. If the activity of the cells that break down bone is greater than the activity of those that build it up, you lose bone mass. This primarily affects the trabeculae (the supporting meshwork of dense bone) found in vertebrae and the ends of our long bones. If the trabeculae disappear, both the bone mass and the strength of the skeleton decrease. This is osteoporosis.

Bone strength

Several components contribute to skeletal strength, bone mass being one. Bone mass can be measured and is then called bone density: directly translated, ‘osteoporosis’ means ‘porous bone’ – i.e. bone that has a reduced density.

Skeletal resilience depends on a number of different factors:

- Bone mass, often called bone density.
- Bone microstructure – the structure of the trabeculae in porous bone and the thickness of the bone cortex (or outer shell).

- Bone metabolism – the renewal and breakdown of proteins that build up the bone tissue.
- Bone macrostructure – the size of the skeleton, i.e. dimensions such as length and volume.
- Bone elasticity – its ability to deform rather than break when exposed to high stress.

In combination, these factors constitute what may be called bone quality – but at present there is no precise measure of quality available for the skeleton. You could say, however, that a fall is a test of quality. If you fall down and don't break anything, your bone quality is good. But if you break a bone when you fall, that shows that strength is impaired due to a change in one or more of the above components.

The qualities of bone change during life, and this is most clearly evident in children's injuries. Children's bones are more elastic (tough) and therefore bend rather than snap across when they are fractured – for example when you try to break off a young branch or a twig of willow (hence the English term 'greenstick' or 'willow fracture'). In the elderly, it is like breaking a dry branch: the bone snaps right across.

How common are osteoporosis and fragility fractures?

Ageing population. Osteoporosis and fractures increase with age; breaking bones, especially, perhaps, breaking a hip (femoral neck fracture), used to be described as a natural part of ageing. Knowledge has increased, and we now recognise that things are not that simple, but nevertheless, fractures do become more common the older we get. Every second woman over age 50 will sustain a fracture at some point during the remainder of her life. With a growing population and an increasing proportion of ever older individuals, the incidence of fractures is expected to rise not only in Sweden, but in many parts of the world. It may be of interest that mean life expectancy in women has risen by 19 years just since 1950; it now stands at 83 years, and is expected to reach 86 by 2050.

Over the last 50 years, Sweden and the western world have seen an almost exponential rise in the incidence of osteoporosis-related fractures. While all types of fractures have increased, the most notable rise has been in hip fractures – the type of fracture that carries the highest cost to society. Every year there are between 16,000 and 18,000 hip fractures in Sweden, although the most recent studies suggest that the increase has levelled off both here and in the USA and Canada.

Common osteoporosis-related fractures

The fractures usually associated with osteoporosis and brittle bones are those involving the hips, wrists, vertebrae and shoulders. Knee fractures are also often associated with brittle bones.

Vertebral compression/vertebral fractures. Vertebral compression or vertebral fractures usually involve collapse and reduced height of the vertebra. Often you are unaware that it is happening, and the first thing you notice is that you have become shorter. However, in some patients it can be directly related to normal daily activities or a small trauma and in this case it triggers acute pain. This means that in some individuals vertebral compression causes only loss of height and a bent back, whereas in others it also leads to a pronounced and chronic pain problem.

Vertebral compression fractures are the fractures most directly linked to osteoporosis, and hence to low bone density, since they can happen without any fall or other trauma at all. Generally, compression fractures first occur about 5–10 years after the menopause and then occur at all ages, which means they are very common in the very old. The fractures can cause vertebral collapse of varying degrees, and it is not unusual to find several collapsed vertebrae in a single patient. Vertebral compression fractures received much attention early on in osteoporosis research and have been evaluated in all clinical trials evaluating drugs to reduce the risk of osteoporosis and fracture.

Fractures of the wrist and upper arm. Wrist fractures are common in children in conjunction with various leisure activities: skating, roller blading, trampolining, riding, football, athletics etc. In women, the next rise in the incidence of wrist fractures occurs around the age of 50, often as a result of a stumble while out walking in the countryside. Women often describe a feeling of unsteadiness – something rarely mentioned by men. While there are no studies that definitely confirm this, there are ongoing studies that are investigating the balance system and differences between men and women.

Upper arm fractures tend to affect a somewhat older age group. You can't stretch your hand out as fast as you used to, and instead injure your upper arm near the shoulder. Usually these fractures are treated with a simple sling to rest the arm, and movement exercises must be started fairly early to prevent stiffness. Even so, it often happens that full mobility does not return when the fracture has healed.

Fractures of the hip and pelvis. Hip fractures mostly affect older individuals; average patient age is just over 80 years. There are two types of hip fracture: fracture of the neck of the femur (the thigh bone) and fracture of the upper part of the femur itself. The fractures are treated differently, using either an artificial hip joint, nails or a plate with a screw. In most cases you can get up and walk immediately after the operation. In some patients the actual hip remains intact but the pelvic ring is damaged. Such fractures are usually on the front of the person. They give pain but do not require surgery.

Underlying causes of fracture

Fracture is the extreme consequence of osteoporosis, but in essence all fractures except vertebral compression fractures are linked to a fall. To make it easier to understand the underlying causes, they can be divided into three main groups: those related to the fall; those

related to the force of the fall; and those related to the resilience of the bone.

In women you generally see the risk of falls starting to increase somewhere around middle age. Usually the patient feels insecure or unsteady. This can emerge even in interviews of women who experience wrist fracture. How you fall is also important: the older you get, the slower your reactions become and the poorer your ability to regain your balance after a misstep. At a relatively younger age you generally have time to stretch out your hands, resulting in wrist fractures. The older you get, the less able you are to react and protect yourself, thus laying yourself open to the more serious fractures around the hip joint.

The forces involved in trauma are very important: it is well known that traffic accidents involving great forces lead to more extensive injuries and more severe fractures. In osteoporosis-related fractures the force of the trauma or fall is much smaller, but still enough. Nevertheless, the forces can vary and, as in sports or athletics, your degree of protection can vary. If you are walking briskly or running and then stumble on a kerb, the risk of fracture is much greater than if you slide down slowly onto a fitted carpet. It is of course well known in this context that greater bodyweight, and thus more fatty tissue, provides protection which can absorb the energy of a fall and reduce the risk of fracture. This knowledge has been utilised in developing hip protectors for the very aged to reduce the risk of hip fracture.

Changes in bone mass during life

Bone density changes throughout life, and women reach their peak bone mass around the age of 20–30 years. How strong your skeleton is at 20 depends very much on hereditary factors, and one of the most important periods for skeletal development is around puberty. This is essentially the time of life when you can have a positive or negative influence on your chances of reaching your peak bone mass, i.e. your maximum potential.

In everyone, bone density diminishes as part of natural ageing. Two factors determine how low the bone density becomes: how much is built up in youth, and how rapidly it is lost with advancing age. From a peak at around age 20–30, bone mass starts to diminish from some point around age 50. Women have less bone and lower bone density than men from the outset, which makes the change more noticeable in women.

Several factors contribute to making the loss of bone mass rapid or slow. An important period in a woman's life is the time around menopause, since falling oestrogen levels further accelerate the loss of bone density. Oestrogen is one of the most important hormones for maintaining bone density, and when oestrogen levels drop, some women lose their bone mass more rapidly because the braking effect exerted by oestrogen on cell regulation is lost.

We still do not know why all women are not equally sensitive to the loss of oestrogen, and we therefore cannot identify those at most risk of suffering the negative effects.

Several other conditions can also lead to reduced bone density. These include illnesses that require long-term treatment with cortisone preparations. Conditions that prevent you taking in or absorbing of all kinds of nutrients from food also increase the risk of developing osteoporosis. The same applies if your mobility is impaired, as in certain neurological disorders.

How can we identify the at-risk patients?

Osteoporosis and osteoporosis-related fractures are thus pathological conditions which have many different causes and can be due to inherited changes in more than one gene (the basic unit of heredity). In this respect osteoporosis is similar to several other major public health problems such as diabetes and hypertension. This means that we are not going to be able to identify a gene that confers fracture, but we will, we hope, be able to identify combinations of genes that work together unfavourably to contribute to a high fracture risk and impaired bone quality, and thus to reduced skeletal resilience.

Health, disease and lifestyle

Sunshine and food. Many different factors can affect the skeleton and the risk of fractures, most of them linked in some degree to age and/or gender. Lifestyle and environmental factors interact here just as they do in many other disorders. Diet is important for everyone, but it is not uncommon to see changes in total nutrient intake over a lifetime. Many of the very aged reduce both their energy and protein intake, so that they lose weight and even become underweight. In an early study we showed that women with hip fractures weighed on average 7 kg less than healthy women of the same age. It is well established that osteoporosis is much less common among those with a higher bodyweight. In 75-year-old women we even showed that bodyweight had a much stronger positive effect on bone density than physical activity and muscle strength. Others have shown that osteoporosis is less common in women weighing over 70 kg.

Calcium is the mineral which gives the skeleton its hardness, and the skeleton serves as the body's calcium reservoir. Calcium plays an important part in the functioning of most body cells, including heart cells. Calcium is therefore necessary as a building block for the skeleton, and the diet should include enough of it, which it doesn't always, especially among the elderly. The recommended daily intake is 800 mg, but in middle age many women stop consuming dairy products – our main source of calcium – and end up with a daily intake around 650 mg.

Vitamin D is produced in the skin from the sun's rays and is then converted to an active hormone in the liver and kidneys. We can also get some from our diet, notably from oily fish such as salmon. In combination with parathyroid hormone, vitamin D regulates the deposit and withdrawal of calcium from the skeleton and thus also calcium levels in the blood. Recently, vitamin D has also been linked to favourable effects on many other tissues. Living relatively far north, our sunlight is limited during the winter months and is in reality insufficient for our needs, but thanks to supplements in certain dairy products we still get a part of what we need. Compared to Scandinavian women, therefore, older women in southern Europe

even have somewhat lower levels of vitamin D. Among older women, we have found the very lowest vitamin D levels in those who basically never go out for a walk or take part in other outdoor activities. However, we have also found that the lower the vitamin D level in older women, the poorer their balance, walking speed and thigh muscle strength. In addition, these women have more fractures. Vitamin D thus affects not only bone tissue, but muscle function and balance as well, and can therefore contribute both directly and indirectly to fractures if it leads to an increased risk of falling. Interestingly, the highest vitamin D levels are seen in women in September, after they have taken advantage of the summer sunlight.

It is thus beneficial also for the skeleton to find a balance between adequate sunlight and diet – perhaps solar food alongside all ingredients from the food pyramid.

Activity and inactivity. If you travel to the moon and are exposed to weightlessness with no chance of exercise, you quickly lose bone mass – a fact soon noted in astronauts. If for any reason you become bedridden for a long period – several months – you lose bone mass. If your leg is in a cast for six months and you are not allowed to put weight on it, you lose bone mass in that leg.

Mechanical load is necessary in order to retain all the skeleton's qualities. The most important benefit of a daily walk is to preserve your bone density and not expose yourself to unnecessary inactivity. Older women who live in the country are fundamentally more active than women who live in town, and there are studies to show that rural women have better bone density and fewer fractures than urban women. The only ones who are marginally better are those urban women who always, regularly, take part in organised exercise. Similarly, we see that older women who lead a physically active life have better muscle strength.

In young women we find that those who enjoyed physical education in school have better bone density than those who thought it was boring.

Tobacco and alcohol. It is well known that smoking has a negative effect on the skeleton. Women who smoke generally have lower bone density than non-smoking women. In middle-aged women we have seen that those who smoke are at greater risk of fractures. In older women who stop smoking we find that bone density gradually approaches the level of non-smokers. More than ten years after giving up smoking, only a minor effect remains. While smoking has a direct inhibitory effect on bone cells, it has also been possible to link some of the negative effect in middle-aged and older women to lower bodyweight among the smokers. This association is interesting in young women.

While smoking does affect the skeleton, these women also tend to be somewhat overweight, which probably counteracts the negative effect to some extent.

Overuse of alcohol often leads to falling injuries and fractures, but light or moderate intake is most likely not of major significance for osteoporosis.

Other illnesses. Other illnesses can contribute to the development of osteoporosis. This applies for instance to gastrointestinal conditions that prevent the absorption of nutrients, such as gluten intolerance or inflammatory bowel disease (ulcerative colitis, Crohn's disease). It also applies to other inflammatory diseases, the most common being rheumatoid arthritis, but individuals with a long history of diabetes are also at greater risk of developing osteoporosis.

It is also common for those who sustain fractures in old age, especially hip fractures, to have several other illnesses and often multiple medications. Someone who also suffers from dizziness or balance impairment after a stroke, Parkinson's disease or similar is at high risk of falling and sustaining further fractures. Recent research findings have now also demonstrated common biological mechanisms between vascular disease, diabetes, obesity and osteoporosis.

Hereditary factors

It is fairly obvious that hereditary factors also play a role in the size of the skeleton: people have always made comparisons between the body height of a child relative to the body height of the parents. Early studies also showed that fractures were more common in a daughter if her mother had suffered fractures. Today the question ‘Has your mother or father had a hip fracture?’ appears on most questionnaires used to estimate the risk of fractures at osteoporosis clinics. This is one of the more significant questions, but it does also show that you had a parent who reached that age: a hip fracture reflects longer survival. Studies on twins also provide unique information about what can be linked to heredity and what is environmentally mediated. Today modern biotechnology allows us to study variation within different genes and discover new genes that control various aspects of the skeleton’s resilience and regulation.

How is osteoporosis diagnosed?

Osteoporosis is diagnosed by the measurement of bone density, and the purpose of the examination is to assess the risk of fracture and thus the need for treatment. Bone densitometry is a form of X-ray examination which allows the mineral content of the skeleton to be determined. The examination is simple, quick and entirely painless. The radiation dose is very low. Bone density is measured in the back and hip, i.e. the sites where fractures commonly occur. Bone densitometry is also used to monitor the effect of treatment.

The first bone densitometers were developed in the early 1960s and allowed bone density to be measured in the wrist. The first whole-body densitometers appeared in the late 1980s and gave access to a rapid and effective method for diagnosing osteoporosis. Bone densitometers, called DXA meters (dual energy X-ray absorptiometry), allow the entire skeleton to be assayed as well as specific areas such as the spinal vertebrae and hips.

The value measured by bone densitometry is related to values from a reference population. Two comparative values are used, one based on young adult women who have attained their peak

bone density, i.e. in the 30- to 40-year age group, and one based on women of the same age as the person examined. These comparative values, which are given in standard deviations, are designated T-score and Z-score respectively, and can best be likened to comparing growth curves in children.

A T-score of -1 or better means that your bone density is normal. T-scores between -1 and -2.5 constitute osteopenia or somewhat reduced bone density, while a T-score below -2.5 constitutes osteoporosis. This has been agreed internationally and in principle allows comparison of data from different countries.

Bone density measurements can also be used to generate knowledge about the body composition in general, i.e. the amounts of fatty tissue and muscle mass in addition to bone mass. This measure is used primarily in studies to acquire knowledge, i.e. for research purposes, but it can also be made use of in patients with anorexia, for example – a condition with major implications for the skeleton.

Drug treatment

Several drugs are now available that can strengthen the skeleton and reduce the risk of future fractures. They act by reducing the breakdown (the most common) or by stimulating the generation of bone. Drugs are available in various forms: as tablets, powder, injections and drips. The treatment duration depends on which drug is used. Standard treatment always includes calcium and vitamin D supplements. Available drugs are most effective in reducing the risk of vertebral compressions, and lead to this risk being halved. The risk of other fractures is also significantly reduced, although measures to reduce the risk of falls must also be taken.

Studies on the significance of heredity

Since heredity determines much of our life and health, it is logical also to examine which hereditary factors have an impact on skeletal resilience. Estimates from twin studies suggest that as much as 60–80 per cent of the volume of bone tissue is related to heredity, i.e. to our genes. These genes are often linked to mechanisms that control the metabolism of skeletal proteins, which in turn regulate bone cell activity. As already mentioned, the skeleton primarily contains three types of cells: osteoblasts, which build the skeleton, osteoclasts, which are related to macrophages and break down the skeleton, and osteocytes, which are embedded in the bone and probably act as transmitters of nerve signals from mechanical stimuli, such as load (e.g. weightbearing). A difficulty worth mentioning in the context of bone studies is the slow rate of bone metabolism – around 8–10 per cent every year, with only 3 per cent per year in the bone cortex – which means that it often takes a very long time to identify changes. Another obstacle is the difficulty of obtaining and experimentally culturing cells from bone tissue, because it is made up of minerals.

The aim of our studies on osteoporosis and fractures in women is:

- to identify the genes associated with a high risk of fracture;
- to identify genes that have a protective role and are therefore linked to high bone mass and a low risk of fractures,
- to evaluate the interplay between genes and environmental factors such as lifestyle changes.

The women in the study. Our study includes a main group of 1,065 25-year-old women. At the same time we are investigating these women's parents and grandparents (maternal and paternal) in order to map hereditary factors in earlier generations as well, above all factors that influence peak bone mass, which is reached between 25 and 30 years of age. We will compare the results in this group with results from women aged 75 years, who thus have already started to lose bone density, and more than 44 per cent of whom have already sustained some form of fracture during their life.

Examinations include measurement of bone density by various methods, determination of body composition, i.e. the proportion of fatty and muscle tissue, and detailed mapping of factors that influence health and lifestyle, not least physical activity and smoking.

Hereditary factors that influence the skeleton. We are studying variation in genes that in different ways influence or regulate the metabolism in bone tissue. This involves genes directly associated with bone metabolism and genes that are linked to regulation or metabolism of adjacent tissues, primarily fatty tissue, and therefore probably are of major indirect importance. We are also studying the significance of genes that are linked to calcium metabolism and influence the effect of sex hormones.

Type I collagen is the most common protein found in bone tissue. Disturbances in collagen metabolism can lead to structural changes which in turn affect the mineralisation of bone tissue. This is most pronounced in a condition known as osteogenesis imperfecta, a hereditary disorder where those affected have specific variants of genes located on chromosomes 7 and 17. We have identified a link between a specific variation in the gene for collagen, where older women with the least common allele (i.e. variant of the gene) have 2.7 per cent lower bone density. This corresponds to the bone density of a woman who is 4–5 years older, and represents a 1.8 times increased risk of one type of fracture – wrist fracture – which may suggest that the change is of functional significance. To investigate this more closely, we are studying the genes' building blocks and how these are converted to proteins in bone tissue from patients with fractures, so that we can also study the protein expression directly.

Vitamin D is a very essential nutrient factor and is important to keep the calcium metabolism in balance. It probably has a broader physiological role and influences the growth and maturation of differences between cells within several cell systems, although the primary target organs are the parathyroid glands, intestines and bones. The effect of vitamin D on bone cells is therefore both direct

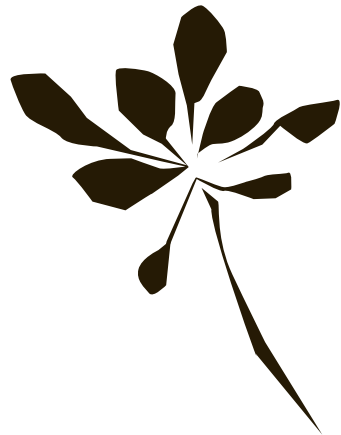
and indirect. When analysing variations in the gene which gives rise to a receptor protein that binds vitamin D, we find an association with bone density, especially in the hip in older women. Interestingly, we also see a link with heel bone density as measured by ultrasound – a measurement considered also to provide qualitative information. We likewise find increased bone resorption when inhibition via oestrogen secretion becomes reduced with the menopause. Consequently, there is a link between the female sex hormone – oestrogen – and bone tissue balance, and it is well known that some women rapidly lose bone tissue immediately after the menopause. The oestrogen effect is strongest in porous bone where cell activity is highest, and in our studies we have also found a connection between variations in the gene for oestrogen and up to 6 per cent lower bone density in the vertebrae of older women with certain particular predispositions.

Summary

Hereditary variations influence skeletal development and the development of osteoporosis with advancing age. The impact of variation in different genes is probably different at different times of life. Some genes contribute to determining what the maximum bone density will be, and others to the post-menopausal rate of loss, while yet others are important for the size of the skeleton. Our association studies demonstrate that several genes that are important in this context have significance for bone mass and fracture. Today we only know a fraction of the genes that are involved and affect the risk of fracture. However, our studies are helping to identify genetic influences both in young women and in the ageing woman. By identifying the genes of greatest importance for developing high or low bone mass, we are able to study both protective factors and risk factors for osteoporosis.

The strength of our studies is that our study groups represent the normal population, and they are large and very well characterised. Studying several generations enables us to come closer to an

analysis of environmental factors as well, and allows us to study the interplay between genes and lifestyle factors. These investigations are supplemented by studies where we have developed a method for analysing the effect of genes directly in bone tissue, meaning that we can also gain information about what proteins are being produced.



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Gender differences in medication use by elderly people

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Equality in care cannot be taken for granted. The National Board of Health and Welfare has pointed to systematic and unwarranted differences in the medical and social care provided to women and to men. Our project aims to take a closer look at these gender differences in terms of utilisation of various medical and social care services by elderly people. We can already show, for instance, that inappropriate medication use is more common in women than in men.

Under the Health and Medical Services Act, care and treatment should be offered on equal terms to all, regardless of age, gender or sexual orientation, functional impediment, place of residence, training, social position, country of birth or religious affiliation. Equitable care should be based on the individual's needs. The National Board of Health and Welfare's monitoring of equality of care has nevertheless pointed to systematic differences between men and women, although it has been possible to see some positive developments in recent years, for instance within

coronary care. Nevertheless, unwarranted differences remain, and appear to become more pronounced with advancing age.

Social justice problems concerning access to care and treatment are accentuated by the fact that older women tend to be in a weaker socioeconomic situation than men of the same age. Although elderly people often have great need of public services in the form of medical and social care, very little research has focused on the very aged and the services they receive. The elderly population is dominated by women because on average women live longer than men.

This project aims to describe the medical and social care received by older women in Sweden. The first step is to describe gender differences in the use of various medical and social care services by elderly people, including the use of prescription drugs and assistive devices. Medical care (going to the doctor, the dentist and the district nurse), hospital visits, home help and sheltered housing will also be described within the project. The use of these services will be studied in relation to different measures of ill health such as illness, disability and cognition. Use of medical and social care will also be studied relative to other factors, such as age, socioeconomic status and civil status, which influence the need and demand for medical and other care.

While most studies of medical and social care utilisation focus on a particular type of service, the present project will describe and analyse several aspects of medical and social care. We expect to find that gender differences vary between different types of services, and that our findings will increase our understanding of how gender differences arise and persist in the utilisation of medical and social care services.

Explanations. There can be numerous reasons for inequality in medical and social care. Women and men differ in many ways. We know for instance that women, despite living longer, need healthcare services more frequently than men in every age group. Older women are generally less well educated than men of the same age; they have often been less active in the labour market and more frequently live

alone. All these factors can influence both health and the approach to seeking care.

Reasons for inequality may also exist within the care system. The first contact person within the system – the ‘gatekeeper’ – can play an important part in how an individual is treated. Some studies have shown that women and men are treated differently even when the clinical picture is the same.

Differences may therefore depend not only on the individual and his or her attitude when seeking help, but also on the behaviour of those providing medical and social care. All this is influenced by the manner in which medical and social care is organised and by the culture and society in which we live. To specify the precise causes of these inequalities is not possible with the quantitative analyses we use. However, it is likely that there is a complex combination of underlying factors.

By describing differences in various types of medical and social care, we hope to see patterns and be able to pick out indications as to what we should take a closer look at, i.e. in what areas women appear to be treated unfairly. We are also interested in identifying areas where men perhaps do not receive the help they need. The project will address such questions as: Given the same age and state of health, what gender differences exist in the utilisation of different types of care? What is the significance of social factors such as education and social support? Does the significance of these factors differ between men and women?

The Swedish Prescribed Drug Register is a goldmine for studying gender differences in the use of prescription drugs, since it includes all drugs dispensed at Swedish pharmacies. In this chapter we will present some results from studies by Kristina Johnell and co-workers that focus on the elderly population. This work on gender differences in medication use has become an important part of the project.

Medications and the elderly population

Prescription of drugs to elderly people today is extensive. Those aged 75 years and over represent about 9 per cent of the population

but consume more than one-quarter of all medications in Sweden. Since the 1990s medication use has been steadily growing in this age group, particularly in sheltered housing facilities, where elderly people now use about ten preparations each on average. Elderly people are more sensitive to medications because of advanced age, cognitive impairment, organ failure and illnesses. At the same time they use more medications than any other age group and therefore have the greatest overall exposure to drug-related risks.

Ageing leads to changes both in the turnover of drugs (pharmacokinetics) and the effect of drugs on the body (pharmacodynamics) (Fastbom J. *Äldre och läkemedel [Older People and Drugs]*. Liber AB 2006). The most important pharmacokinetic change is reduced kidney function, which is very common in elderly people. While reduced kidney function is part of normal ageing, it can increase the risk of adverse effects of drugs. This is because the kidneys are responsible for ensuring that harmful substances and waste products leave the body through the urine – a process known as elimination. When kidney function is impaired, the elimination of certain drugs (e.g. digoxin) will be slower and the drugs therefore remain longer in the body, where they accumulate, leading to adverse drug effects. Liver function also deteriorates somewhat in advanced age. Blood flow in the liver diminishes and some enzyme systems change. This means, for example, that diazepam is metabolised more slowly in an older person than in a younger, resulting in a risk of adverse effects. However, age-related liver changes are regarded as of less pharmacokinetic importance than the deterioration in kidney function.

Body composition also changes as we get older: muscle mass diminishes and the proportion of body fat increases. Drugs that are distributed in fat can thus become more widely dispersed and remain in the body for longer. This is why older persons can feel drowsy the day after taking sleeping drugs of the benzodiazepine type.

An important age-related pharmacodynamic change is that the brain and nervous system become more sensitive to medications at an advanced age. This increases the risk of adverse effects of drugs

that act on the central nervous system, for instance psychotropics, anticholinergics and morphine-related analgesics, i.e. opioids. Blood pressure regulation also deteriorates with age, making elderly people more sensitive to antihypertensive drugs. In the worst case, antihypertensives can cause an older person to faint because of a rapid fall in blood pressure. Another age-related pharmacodynamic change involves the gastrointestinal tract. Gastric mucosal protection is less efficient in old age, meaning that medications which irritate the stomach, such as anti-inflammatory painkillers, more often cause ulcers in older individuals than in those who are younger. Constipation is also common in elderly people, so drugs that cause constipation as a side effect, such as opioids, should if possible be avoided.

Overall, age-related pharmacokinetic and pharmacodynamic changes mean that many medications have a different and often stronger effect in older than in younger persons. Moreover, many drugs are not tested in older subjects in clinical trials when new medications are being developed, meaning that recommended dosages are based on younger persons and may therefore be inappropriate in an older person. For drug treatment of elderly people, it is generally recommended to ‘start low, go slow’ – in other words, start with a low dose and increase it slowly where necessary, in order to prevent adverse drug effects.

Quantity. Drug treatment in elderly people is complicated by the fact that they often have several illnesses (multi-morbidity) and frequently require concurrent treatment with several medications. Use of multiple drugs (polypharmacy) is in itself a significant risk factor for medication problems such as adverse drug reactions. Polypharmacy is moreover often linked to inappropriate medication use, for instance when a preparation is used for a non-existent or incorrect indication, or when inappropriate drugs or medications that counteract each other are used. In recent years, studies have shown that adverse drug effects and polypharmacy can cause acute hospital admissions among elderly people. It is important to note

that most of these adverse drug effects are seen as preventable; in many cases they can be linked to deficiencies in the prescription and monitoring of drugs.

Quality. The National Board of Health and Welfare has developed a proposal for quality indicators to assess the quality of drug therapy in elderly people. These quality indicators fall into two groups. Drug-specific indicators describe quality in terms of the selection, dosage and combination of drugs. Diagnosis-specific indicators describe the incidence of rational, irrational and inappropriate or hazardous prescription of drugs for the most common diagnoses in older individuals.

The indicators are intended to be used both when monitoring how effective a drug is and when taking measures to improve treatment, such as in patient medication reviews. The indicators are now well known throughout Sweden and applied in various ways in the effort to raise the quality of medication use among elderly people.

The National Board of Health and Welfare's quality indicators have also proven very useful in various epidemiological drug studies. Our research group has published several studies on inappropriate medication use in elderly people based on these indicators.

The Swedish Prescribed Drug Register in studies of medication use in the elderly population. The opportunities for national register-based epidemiological drug studies improved significantly with the inception of the Swedish Prescribed Drug Register on 1 July 2005. This register is one of the largest individual-based epidemiological drug databases in the world, and is more comprehensive than the corresponding registers in many other countries. The register contains individual-based data on medications dispensed at pharmacies (both prescriptions and multi-dose drug dispensing (apodos, see Fact box 1). The Swedish Prescribed Drug Register is well suited to studies on medication use in elderly people, since a large proportion of drugs used in older patients are dispensed

on prescription or in multi-dose (apodos) packages. Information on medications dispensed is recorded at the pharmacies and then transferred to the National Board of Health and Welfare, which maintains the register. The register is intended for use in epidemiological studies, research and generation of statistics in the medical and healthcare field. The Prescribed Drug Register can be record-linked to other Swedish registers in order to study medication use in relation to other factors such as educational level and various diagnoses. We have amongst other things been able to study the significance of education and its influence on the extent and quality of medication use among elderly people. This has shown that poorly educated elderly people more often take several drugs concurrently and are more exposed to inappropriate drug combinations.

Gender differences

One often hears that there are large differences between the genders in terms of pharmaceutical effects and adverse drug reactions. The Medical Products Agency nevertheless suggests that gender differences related to turnover of drugs in the body, efficacy and safety are often small. It is thus something of a myth that adverse drug reactions differ greatly between men and women. On the other hand, it is a well-known fact that women generally use more medications and seek care more often than men.

We speak of the so-called gender paradox: the fact that women on average report more symptoms of illness and more often seek care during their lifetime, but at the same time women have a higher life expectancy than men. Women also report adverse drug reactions more often than men, possibly because they use medications more and have more frequent contact with the healthcare system than men. Closer analysis of medication patterns reveals that women use more psychotropics and analgesics while men use more cardiovascular drugs, which could reflect gender differences in disease incidence or diagnosis. It is known that women and men have different disease patterns, and that diseases – e.g. myocardial infarction – may present differently between the genders. Women

and men may also describe symptoms differently (Johnell K. 'Könsskillnader i läkemedelsanvändning' ['Gender differences in drug use']. *Äldre i Centrum* No. 1/09, 2009).

Another common notion is that clinical trials of new pharmaceutical substances are performed mainly in men. The reason may be that the earliest trial phase (Phase I), which only comprises healthy individuals, is sometimes carried out only in men, partly because of the perceived risk of testing a new pharmaceutical substance in women before it has been established whether the substance can damage an embryo or fetus. However, when it comes to testing in patients, most studies nowadays include both genders. Gender distribution in clinical trials is determined primarily by the gender-specific incidence of the disease for which the drug is intended. The few clinical patient trials that are limited to one gender concern drugs intended for use only in women or only in men, for instance oral contraceptives. The Medical Products Agency makes an assessment of the gender representation, and of any gender differences, in the documentation before a new drug is approved for marketing. A drug must show a positive balance between benefit and risk in both women and men before it is approved for use in both genders.

Inappropriate medication use. We have analysed some of the above-mentioned drug-specific quality indicators of the National Board of Health and Welfare in respect of the use of anticholinergics, long-acting benzodiazepines, concurrent use of three or more psychotropics (drugs for mental disorders) and serious drug interactions. Anticholinergics inhibit the effects of acetylcholine on the peripheral and central nervous system and are found in several different drug classes, including the older type of antidepressants and antipsychotics. Medications with anticholinergic effects should be avoided in older persons, especially patients with dementia. Adverse anticholinergic drug reactions include dry mouth, blurred vision, constipation, cognitive disturbances and confusion. Benzodiazepines are used as tranquillizers and sleeping drugs. Long-acting

benzodiazepines remain in the body for a long time before being eliminated. This can lead to drowsiness, dizziness and accidental falls in elderly people, since the long-acting benzodiazepines remain even longer in the body of an older person than in a younger one. Concurrent use of three or more psychotropics carries a special risk in older individuals because the ageing central nervous system is extra sensitive to adverse drug effects, and the burden of several psychotropics may become too much for the ageing brain. Drug interactions (i.e. inappropriate combinations of medications) can lead to adverse reactions and hospital admissions among elderly people. Older individuals are more fragile and more prone to adverse drug reactions than younger people, but at the same time they also use more medications than any other age group. Taken together, this means that elderly people are those most exposed to hazardous drug interactions.

Our drug register analyses of medication use in over 600,000 elderly individuals (aged 75–89) have shown that inappropriate medication use (measured by the National Board of Health and Welfare's quality indicators) is more common in women than in men. One in four women had some form of inappropriate medication use compared to one in five men. Women were more likely to be given inappropriate drugs than men, even after taking into account gender differences in age, education and number of medications. Women live longer, use more medications and have a lower educational level than men. However, in our analyses we have been able to take these differences into account by adjusting for age, education and number of medications, so the gender differences seen in our results are not explained by these factors.

In particular, women were more likely to be exposed to inappropriate treatment with psychotropics: psychotropics with anticholinergic effects, long-acting benzodiazepines and concurrent use of three or more psychotropics. Women were nevertheless at lower risk than men of being exposed to serious drug interactions, probably because of their lower use of blood-thinning agents, which often interact with other drugs.

Psychotropics and dementia medications. We have seen that older women generally have a greater tendency to use sleeping drugs and tranquillizers of the benzodiazepine or benzodiazepine-related type. However, women appear to receive less up-to-date treatment with these drugs than older men. Our register analyses have also shown, after taking into account the higher medication use in women, that older women are somewhat less likely than older men to be given newer drugs. This phenomenon is difficult to interpret, and more in-depth analysis is needed to identify the underlying reasons. Using drug register data, we have also found that women are as likely as men to be treated with memantine, a drug used in moderate to severe Alzheimer's disease. This finding may seem slightly surprising, since studies have shown older women to be at greater risk of developing dementia than older men.

Of advantage to older women. It is important to point out that women do not always receive unfavourable drug treatment compared with men. In our studies of the Swedish Prescribed Drug Register we have seen that older women treated with NSAIDs have a better chance than older men of receiving concurrent medications to protect the stomach. Stomach-protecting medications are often needed in older patients being treated with NSAIDs to prevent ulcers. As previously stated, older women are also at lower risk of serious drug interactions than older men, probably because of their lower use of blood-thinning drugs, which often interact with other medications.

Reasons for gender differences in medication use. Using register studies, it is unfortunately difficult to obtain information about underlying causes of gender differences in medication use that cannot be explained by gender differences in disease prevalence. However, we may speculate about several possible explanations that could be related to both the patient and to the prescribing doctor. Studies have, for instance, shown that health care consumption (especially primary care) is higher in women than in men. Women and men

express themselves differently, report symptoms differently and probably also are treated differently – encounter different behaviour – within the healthcare system. Socioeconomic status may also play a part, since women, at least elderly women, often have a lower income and educational level than men. Socioeconomic status may be linked to expectations, communication skills, how well informed you are about various treatments, what demands you place on healthcare and how you are treated within the healthcare system. It is therefore important to consider socioeconomic status (e.g. education level) in analyses of gender differences, especially among elderly people. Time will have to tell whether gender differences in medication use will level off as women continue to catch up with men in socioeconomic status and lifestyle.

Future research

Our results show how important it is to analyse women and men separately in future studies of medication use. The healthcare system should provide care for everyone on the same terms. Interest in evaluating whether we are providing equitable healthcare is growing, and equitable healthcare means that everyone should have the same right to safe and effective drug treatment. Research on gender differences in medication use should be more attentive to possible underlying explanations, such as gender differences in socioeconomic status and lifestyle. It is also important to study the interplay between patients and prescribers in detail to determine whether the reason for gender differences in drug treatment is that men and women express themselves differently and encounter different behaviour from healthcare staff. It would also be interesting to explore the real consequences of gender differences in medication use in terms of morbidity and quality of life. The Swedish Prescribed Drug Register will undoubtedly continue to play an important role in studies of gender differences in medication use since it allows the use of specific drugs to be studied with great precision: a task which can be difficult when using smaller databases with fewer users of each individual medication.

Fact box I

Medications and concepts

Apodos: Multi-dose drug dispensing. The patient's medications are packaged and dispensed in pouches containing all the medications that the person should take on one occasion.

Benzodiazepines: E.g. oxazepam, alprazolam. Used as tranquillizers and sleeping drugs.

Benzodiazepine-related drugs: E.g. zopiclone, zolpidem. Sleeping drugs.

Diazepam: A long-acting benzodiazepine.

Digoxin: Digitalis. Used in heart failure, atrial fibrillation and irregular heart activity.

Drug interaction: When two or more drugs taken concurrently influence each other's effects.

NSAIDs: E.g. ibuprofen, diclofenac. Nonsteroidal anti-inflammatory drugs.

Polypharmacy: Concurrent use of several different drugs.

Psychotropics: Collective name for medications used in mental disorders.

Fact box 2

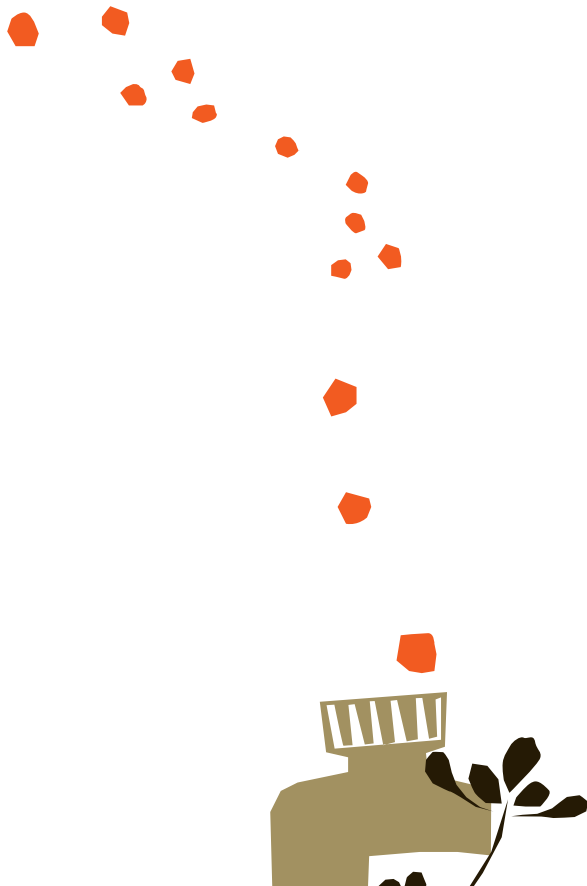
Inappropriate medication use based on the National Board of Health and Welfare's quality indicators for drug therapy in the elderly population

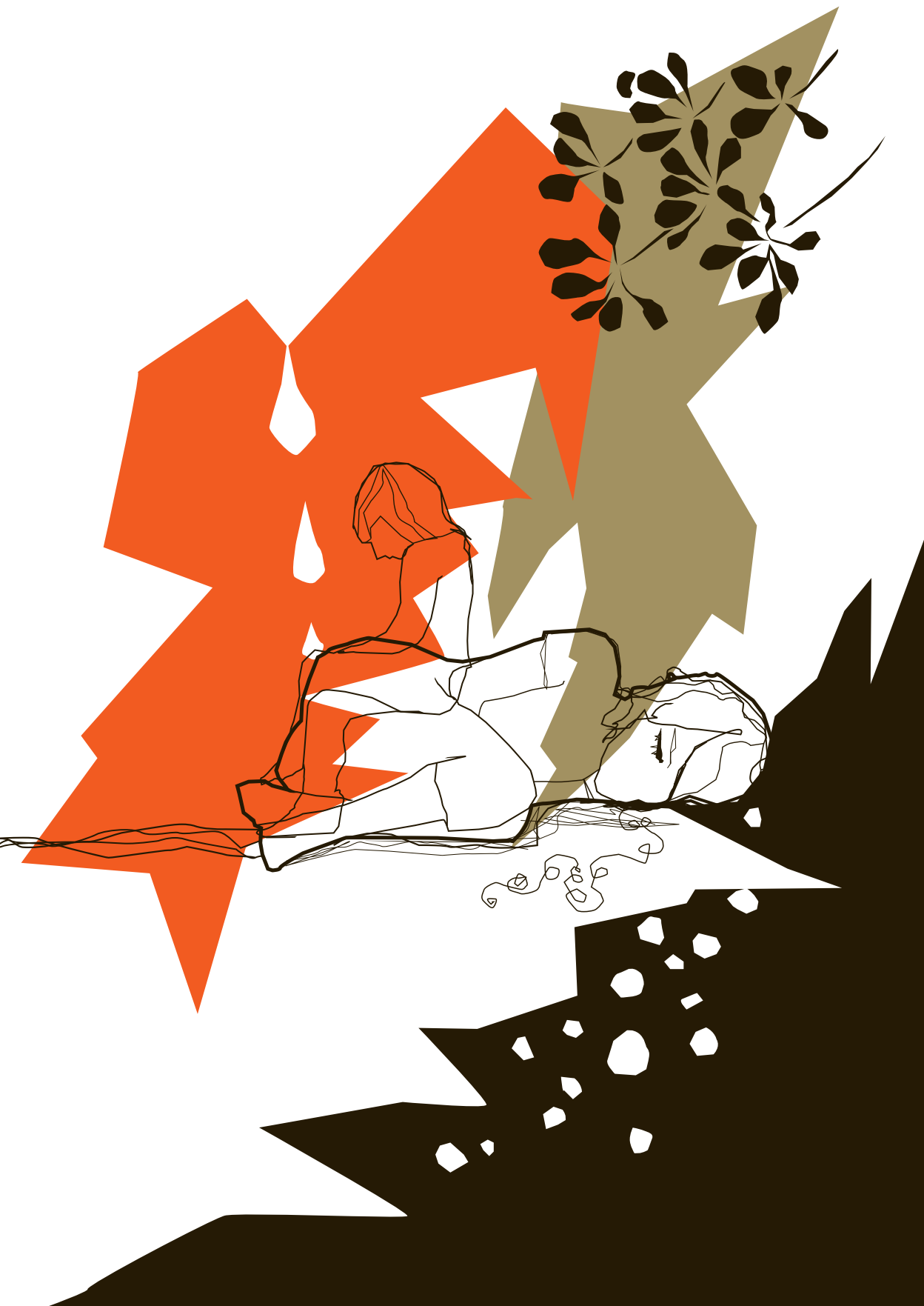
Anticholinergic drugs: E.g. neuroleptics (e.g. levomepromazine), tricyclic antidepressants (e.g. clomipramine) and anti-Parkinsonian drugs of the anticholinergic type (e.g. biperiden).

Long-acting benzodiazepines: Diazepam, flunitrazepam and nitrazepam.

Concurrent use of three or more psychotropics: Use of neuroleptics, tranquillizers, sleeping drugs and antidepressants.

Serious drug interactions: Combinations of medications that should be avoided according to FASS (Pharmaceutical Specialities in Sweden), so called type D interactions.





Women, hormones and mental ill health

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What is the connection between mental ill health in women and the fact that they are women? There may be several explanatory factors to this question; in this research project we have chosen to look at the link with reproduction – in other words, the influence of female sex hormones. Our starting point is the fact that women’s greater vulnerability to depression and anxiety is so clearly associated with their reproductive years.

Depression and anxiety disorders are more than twice as common in women as in men; it is estimated that a woman’s risk of experiencing depression at some point in her life can be as high as 50 per cent. There is a connection between these disorders and events in a woman’s life that are related to her reproductive ability, i.e. the possibility of having children. Especially vulnerable periods are the time of first menstruation, the period after delivery and the two years before the final menstruation (menopause).

There are a great many other explanations for why women develop depression and anxiety disorders more often than men. These include socioeconomic factors as well as Women, hormones and mental ill health healthcare consumption and heredity. However, a growing number of studies also point to actual biological differences between the sexes in the manifestation of genetic vulnerability to mental ill health.

Sex-specific or gender differences with respect to major depression (i.e. one that is not caused by environmental factors) are most pronounced during a woman's reproductive years, i.e. from puberty until she reaches the menopause. Even when other contributing factors are included, the gender differences cannot be fully explained and we must therefore also look for an explanation that has to do with hormones and hormonal effects in the brain. Our hypothesis is that the female sex hormones oestrogen and progesterone act on the central nervous system, leading to increased vulnerability to the development of anxiety and depressive disorders among women.

Female hormones

To understand this vulnerability one first has to understand the function of the female hormones. A woman has two endogenous female sex hormones: oestrogen and progesterone. For obvious reasons, oestrogen is the best-known female sex hormone and we often speak – somewhat casually – of women being ‘on oestrogen treatment’. In reality, it is only women whose uterus has been removed who may receive treatment with oestrogen alone. Most women who are treated with oestrogen also receive some form of synthetic progesterone (gestagen) to supplement the oestrogen. One reason for giving a gestagen is to protect against complications such as irregular bleeding and cell changes in the uterus.

Oestrogen is commercially available in two different forms, as a pharmaceutical containing natural endogenous (although synthetically produced) oestrogen (oestradiol), and as synthetic oestrogen (ethinyl oestradiol). Oestradiol is used primarily to treat

women with menopausal complaints, while ethinyl oestradiol is the most common oestrogen found in oral contraceptives.

While oestrogen has various effects on the body which women perceive as positive, there are of course also certain adverse effects which complicate its use. Oestrogen contributes to development of the female body shape and other sex characteristics during puberty. It has a positive influence on bone density both during growth and later in life, is effective for reducing sweating and hot flushes during menopause, and has positive effects on sleep in postmenopausal women. Negative effects of oestrogen, particularly in the treatment of menopausal women, are an increased risk of breast cancer after long-term use, and a higher risk of thrombosis.

Progesterone is not available as a pharmaceutical because it is difficult to administer in tablet form. When progesterone is taken by mouth, most is broken down and metabolised in the body on its first pass through the liver. The only application for endogenous progesterone is in the form of vaginal tablets given to women undergoing in vitro fertilisation. For all other therapies, whether as hormone treatment of menopausal women or in oral contraceptives, synthetic progesterone – a gestagen – is used.

There is a plethora of different gestagens that have slightly different pharmacological properties. Adverse effects may therefore vary somewhat, for instance between different oral contraceptives.

Hormone levels change in various ways over a woman's reproductive life. Even during a menstrual cycle, the levels of oestrogen and, especially, progesterone undergo a regular pattern of change. The follicular phase of a menstrual cycle, i.e. the period before ovulation, is characterised by preparations for ovulation and dominated hormonally by the production of oestrogen. During the follicular phase there is essentially no production of progesterone. By contrast, the luteal phase of the menstrual cycle, i.e. after ovulation, is characterised by an almost hundred-fold increase in progesterone levels as the body prepares for fertilisation and possible pregnancy. Oestrogen is also produced during this second phase, although the levels are lower than in the follicular phase.

When a woman becomes pregnant, her oestrogen and progesterone levels rise even further. Compared to peak levels during a menstrual cycle, there is a further approximately fifty-fold rise in progesterone levels, while oestrogen levels rise about ten-fold. Hormone levels increase gradually during pregnancy and peak just before delivery. During pregnancy, oestrogen and progesterone are primarily produced in the placenta. This causes a very dramatic drop in hormone levels after delivery when the placenta is discharged. Hormone levels are halved within 24 hours and return within 3 days to levels found during a normal menstrual cycle. If the woman is breast-feeding, the breast-feeding hormones will inhibit ovulation and cause her oestrogen levels to drop within a few weeks to those of a menopausal woman. When menstruation returns after childbirth, hormone levels have normalised.

In the years immediately before menopause, ovarian function gradually starts to decline. First to fail is generally the production of progesterone, which the woman will experience as irregular menstrual cycles and an increased tendency to breakthrough bleeding. When oestrogen levels start to drop, the woman instead develops menopausal complaints such as hot flushes and sweating. While some start having menopausal symptoms even before menstruation has ceased, they generally occur after the woman has stopped menstruating. When more than twelve months have passed since the last menstruation, the woman has entered menopause.

Hormones and the brain

Both oestrogen and progesterone have fundamental effects on the central nervous system. Most studied are the effects relating to reproductive ability and regulation of the menstrual cycle. However, hormones influence sex differentiation in the brain even in the fetus. In rodents, oestradiol and progesterone are of fundamental importance for sexuality and reproduction, whereas in women sexuality is influenced by a number of other factors.

Oestradiol and progesterone can influence nerve cells in the brain in various ways, and these hormones have several types of

receptors both in the nucleus and on the surface of the nerve cell. It is only when a hormone binds to its receptor that it exerts an effect. Oestradiol and progesterone receptors are plentiful in areas of the brain that are important for mental health, the amygdala perhaps being the most familiar.

Progesterone can also affect the brain in another way which may be very significant for mental health. When progesterone is broken down in the liver, active metabolites are formed which have their own effects on the brain, separate from the effects of the progesterone. Progesterone metabolites are known collectively as neurosteroids. The best studied neurosteroid is allopregnanolone (Sundström Poromaa 2003). Allopregnanolone exerts its effect by binding to the GABA_A receptor and therefore influences the GABA system, the brain's major inhibitory neurotransmitter system. The GABA system is sometimes likened to the brain's police force: its task is to monitor other nerve cell activity and extinguish any centre of unrest. It is estimated that about 25 per cent of all communication between nerve cells in the brain uses GABA as a signal substance.

From the woman's – and the mental health – perspective, neurosteroids are important. The easiest way to understand this is to realise that anxiolytic drugs, sleeping pills (benzodiazepines) and alcohol all bind to the GABA_A receptor. Neurosteroids such as allopregnanolone therefore have similar short-term effects to benzodiazepines: they make you tired, reduce your anxiety and can affect your memory. However, just as long-term use of sleeping drugs can lead to addiction and withdrawal symptoms, variations in neurosteroid levels can also cause tolerance and withdrawal symptoms to develop. Allopregnanolone serum levels co-vary with variations in progesterone, which means that elevated values are found both in the last two weeks of the menstrual cycle and during pregnancy. As with progesterone, allopregnanolone levels also fall very rapidly in the first days after childbirth.

Although neurosteroid effects in women have been poorly studied, our group has been able to show that rapid administration of allopregnanolone to women causes profound sedation (Timby

2005). We have also found that allopregnanolone influences certain memory systems in women (Kask 2008). However, the memory effects we observed should be seen in relation to the dose given and the mode of administration. In our experiments the women were exposed very rapidly to neurosteroid concentrations that are only found in advanced pregnancy. In real life, normal variations in neurosteroid levels during a menstrual cycle are unlikely to affect the woman's memory, and it is also likely that over the course of a pregnancy women develop tolerance to the effects of neurosteroids. This agrees well with the findings of numerous studies in which no changes in memory function or concentration ability were seen during the menstrual cycle or during pregnancy in healthy women.

Neurosteroids are generally believed to have an anxiolytic effect, and this has indeed been confirmed in typical animal models of anxiety. However, it is not clear that neurosteroids always act like anxiolytic drugs (Sundström Poromaa 2003). With repeated treatment, increasing symptoms of anxiety are seen instead, and it appears that the anxiolytic effect may be dose-dependent. Studies have also shown that continuous neurosteroid treatment results in the development of tolerance, which in turn leads to withdrawal symptoms when the treatment is stopped. While we do not know whether neurosteroids have an anxiolytic or anxiogenic effect in women, one question occupying our research group is the fact that a small number of women react differently to neurosteroids than the majority do.

The effect of endogenous hormones on mental ill health and mood

Oestrogen is generally associated with heightened physical and mental well-being in women, although it has not been determined that these changes are really caused by the oestrogen itself. The effect of oestrogen on quality of life is most likely secondary. The point is rather that oestrogen alleviates menopausal symptoms such as hot flushes and sweating.

Progesterone has mainly been linked to various negative effects, primarily negative mood effects during the menstrual cycle, but also to the negative mood effects experienced during use of oral contraceptives.

Nearly all women are affected in some way by their menstrual cycle. Over 90 per cent experience change in at least one symptom during the menstrual cycle. Most commonly reported are changes in physical symptoms such as increased breast tension and a sense of bloating in the week before menstruation. Many women also report exacerbation of certain mental symptoms such as irritability and depressed mood during the luteal phase, i.e. the time after ovulation. It has been difficult to develop reliable data on the prevalence of premenstrual complaints of a more mental nature since there is a major difference between what is reported retrospectively and what can be confirmed if the woman enters her symptoms in a diary. Several studies show that among women who state that they have premenstrual complaints, these are only confirmed in 25–40 per cent of cases when the women are asked to rate their symptoms during the next two menstrual cycles.

Severe premenstrual complaints are defined in the psychiatric diagnostic manual as premenstrual dysphoric disorder (PMDD). Premenstrual dysphoric disorder occur in about 3–5 per cent of menstruating women and are characterised by more pronounced manifestations involving at least five premenstrual symptoms and a requirement that the symptoms must have a negative impact on the woman's life and ability to function. From a research standpoint, the definition of PMDD represented a step forward, since it resulted in more uniform definition of the patient group as well as allowing systematic evaluation of different treatment options. One outcome is that we now have several good, very well evaluated treatments for premenstrual dysphoric disorder.

Typically the manifestations consist of mental symptoms such as depression, irritability, anxiety or agitation, mood lability, concentration problems, diminished or increased appetite, loss of energy, and physical symptoms such as breast tension, swelling

or headache. There is no symptom that is unique to PMDD; most of the stated symptoms are also criteria of anxiety or depressive disorders. Many women with PMDD likewise meet the criteria of major depression, except for the time aspect, which is pinpointed to the luteal phase (period after ovulation). It is therefore central to a PMDD diagnosis that a time relationship can be established with the luteal phase of the menstrual cycle.

PMDD has numerous links to both depressive and anxiety disorders. We know that up to 35–50 per cent of women with PMDD have a history of major depression. Twenty-five per cent of the women have experienced depression in conjunction with childbirth (known as postpartum depression). Studies have also shown that PMDD is in itself a risk factor for future depression, on a level with having a history of depression or a genetic predisposition for depressive disorders. Our studies have furthermore shown that women with PMDD are more prone to neurotic personality traits, which also increase the risk of developing depression. Another important similarity between PMDD, major depression and anxiety syndromes is that all these conditions respond to the same drugs. There is now a great deal of evidence showing that serotonin reuptake inhibitors (SSRIs), which are used in depression, also work in PMDD. However, the mode of action of SSRIs appears to differ between these conditions. While it takes three to four weeks before symptomatic relief is obtained in major depression, symptoms of PMDD may resolve after one or two days. This is also the rationale for using cyclical SSRI treatment in PMDD, i.e. the medication is only given in the weeks when symptoms are experienced.

There is another interesting link between PMDD and panic anxiety. Various substances that under experimental conditions can induce anxiety attacks in patients with panic anxiety also trigger anxiety in women with PMDD. By contrast, healthy women in a control group remain completely unaffected by these provocations. Our research has also shown that both patients with panic anxiety and those with PMDD suffer from a functional impairment of the GABA system which manifests itself clinically by a reduction in the

effect of drugs such as benzodiazepines (Sundström Poromaa 2003). Signs of increased activation in the part of the brain known as the amygdala have also been found in women with PMDD, as they are in patients with various anxiety syndromes.

Apart from the fact that PMDD caused the women affected a great deal of suffering, it is also an important model of how sex steroids interact with the central nervous system (CNS) and how sex hormones can influence the development of anxiety and depressive disorders. The sex hormone most strongly associated with PMDD is progesterone, but it is important to stress that a large number of studies have shown that women with PMDD have neither more nor less progesterone or other hormones, including neurosteroids, than do healthy women.

The link between PMDD and progesterone is based on the fact that symptoms arise only in the luteal phase, when progesterone production is highest. During menstrual cycles without ovulation, whether spontaneous or the result of treatment, the patient's complaints disappear. Treatment with anti-progesterone has been tried in PMDD but without success, most probably because the treatment was given at too low a dosage or too late in the luteal phase.

However, oestrogen probably also affects the severity of symptoms. It has for instance been shown that PMDD patients feel worse during cycles with high oestradiol levels than during cycles when levels are low. We have been able to show that, while it is progesterone that has the decisive impact in symptom provocation, the amount of oestrogen also matters. In women whose endogenous hormone production has been reduced to a minimum by means of drugs, the symptoms induced by combined oestrogen and progesterone treatment are more pronounced if a higher rather than a lower dose of oestrogen is used (Segeblad 2009). We have also been able to provoke PMDD-like symptoms in postmenopausal women by giving them oestrogen and progesterone/gestagen regimens that simulate the hormone levels of a menstrual cycle. In postmenopausal women, the most pronounced symptoms are

seen during and shortly after the gestagen is added. We also find that high doses of oestrogen combined with a synthetic gestagen induce more symptoms than low doses of oestrogen combined with a gestagen. For the individual woman this means that low doses of oestrogen are preferable, and that the gestagen supplement should be taken as infrequently as possible if adverse mood effects occur: so-called long-cycle therapy. A possible mechanism which our group has studied is the effect of progesterone withdrawal. Women with severe premenstrual complaints, women who experience adverse mood effects with oral contraceptives, women on sequential oestrogen–gestagen therapy and, not least, women who have recently given birth experience the most pronounced symptoms when the progesterone levels fall (Sundström Poromaa 2003). While the menstrual cycle only affects a small proportion of women, over 70 per cent of all new mothers will be affected by transient symptoms of depressed mood about 2–4 days after delivery ('postpartum blues'). We may therefore assume that small variations affect only a small number of women, whereas large, drastic changes in progesterone levels in conjunction with childbirth affect the large majority. Animal experiments have shown that when progesterone levels drop at the end of progesterone treatment, the animals develop withdrawal symptoms such as increased anxiety and a greater tendency to epileptic seizures. These symptoms are not unlike those observed for instance on withdrawal of benzodiazepines or alcohol.

Animal experiments have shown that withdrawal symptoms can be explained by changes in the GABA system induced by progesterone treatment. Similar changes are also found in women. In patients with certain forms of epilepsy, seizures are more common in the period immediately following a drop in progesterone levels. Falling hormone levels are also believed to explain the increased incidence of migraine attacks during menstruation.

Menopausal oestrogen therapy

In addition to a widespread fear of treatments that include hormones (oral contraceptives and menopausal oestrogen therapy), there are

also in existence a number of beliefs about hormone treatment that are poorly founded.

Menopausal oestrogen therapy is deemed to have beneficial effects on a woman's health and well-being. However, as already mentioned, this effect is probably secondary to the effects of the hormone therapy on the woman's menopausal symptoms (such as hot flushes and sweating) and sleep disturbances.

It has been found that falling oestrogen levels around the time of a woman's last menstruation are associated with a rise in depressive symptoms, although most appear to be linked to sleep disturbances. What does seem clear is that the last one or two years before menopause are a time when the risk of developing depression is clearly raised (Wihlback 2005).

A number of international studies have tried to prove that oestrogen has an antidepressant effect and could therefore be used as monotherapy or to supplement regular antidepressant treatment in menopausal women (Wihlback 2005). In most clinical trials where postmenopausal women have received oestrogen therapy for clinical depression, oestrogen has been found no more effective than placebo. By contrast, a certain positive effect of oestrogen is suggested in studies on women still in the menopause who are diagnosed with depression. However, in the one study so far to compare oestrogen and an SSRI, the SSRI was found to be more effective than oestrogen. A weakness of the studies is also that differences between treatment with oestrogen alone and oestrogen in combination with gestagen have not been examined.

Oral contraceptives

Oral contraceptives have been available for fifty years and their importance for women's equality and sexual freedom is uncontested. The introduction of oral contraceptives may be reckoned as one of the most significant medical advances to emerge in the last century. But where the first generation of women rejoiced in being able to have sex without the risk of pregnancy, today's young women have a refreshingly critical attitude to their oral contraceptives. This is

reflected in clinical practice, where adverse effects which an older generation was prepared to live with are not necessarily acceptable to young women of today. Probably a young woman's choice of contraception is also influenced by a certain mythology around the negative effects of oral contraceptives. This mythology in turn has its origin in the methodological difficulties surrounding research on the effects of contraceptives.

Oral contraceptives are often associated with adverse mood effects and adverse sexual effects. How often mood effects are really caused by oral contraceptives is essentially unknown. In studies where depression and anxiety syndromes have been monitored from the initiation of oral contraceptives up to one year of use, it has been found that about 10–15 per cent of all users report symptoms such as depressed mood, increased irritability and increased agitation. Nearly all women report no mood changes or an improved sense of mental well-being.

In retrospective studies of former oral contraceptive users, the women as a rule report higher rates of anxiety and depression during treatment, but these studies must be considered less reliable. Adverse mood effects and adverse sexual effects are also the most common reason for stopping treatment with combined oral contraceptives despite continuing need of contraception. Women who stop taking their oral contraceptives because of adverse mood effects are thus at increased risk of unwanted pregnancies, and consequently also at higher risk of requiring a legal abortion. Our studies show that women who stop because of adverse mood effects run a clearly higher risk of having an abortion compared to women who stop for other reasons.

The true incidence of adverse mood effects with oral contraceptives is essentially unknown in the absence of placebo-controlled clinical trials. It has in the past been considered ethically untenable to conduct placebo-controlled studies of oral contraceptives since participants would be exposed to the risk of an unwanted pregnancy. This is a dilemma today for contraception

counsellors, because it makes it difficult to determine which effects are drug-related and which are caused by mental health issues that are not related to medication. There are about 400,000 oral contraceptive users in Sweden, most of them in the 15- to 25-year age group. This age also coincides with the time in life when women for the first time risk developing major depression and/or anxiety syndromes. For the individual woman it is hard to determine which adverse effects are caused by oral contraceptives and which are attributable to life itself.

We have studied the incidence of mental ill health in oral contraceptive users with different experiences of their contraceptive. About 30 per cent of women who experienced adverse mood effects during ongoing use of oral contraceptives had an anxiety or depressive disorder. More remarkable, however, is the fact that this figure was just as high in women who stopped taking oral contraceptives because of adverse mood effects. Since this was a cross-sectional study, it is impossible to draw any conclusions about a causal relationship, but our working hypothesis is that if oral contraceptives really had been the cause of the women's adverse mood effects, the incidence of depression and anxiety should have been lower in users who stopped taking their oral contraceptives (Segeblad 2009).

While it is important to clarify the effects of oral contraceptives on mood and mental ill health, it is of course also important to evaluate the actual effects of oral contraceptives on the central nervous system, not least in order to lay a foundation for improved hormonal contraceptives for tomorrow. Our data also show that women who experience adverse mood effects from their oral contraceptives demonstrate actual biological changes in the brain which could indicate that the hormones administered influence the dopamine system and a placebo-controlled functional magnetic resonance imaging study is in progress.

Vulnerable periods in a woman's fertile life

During periods of major reproductive changes, women are especially vulnerable and more easily develop depression and anxiety disorders. Pregnancy and childbirth for instance result in major hormonal, mental and physical stress, and we have primarily focused our research around depression in conjunction with childbirth (postpartum depression), a time when the affected women have natural contact with the gynaecology department.

Postpartum depression is one of the most studied depressive disorders. Apart from the risk of developing this particular form of depression, which is around 10–12 per cent in the industrialised countries, the period after childbirth is also linked to increased vulnerability for onset or deterioration of a number of anxiety syndromes including generalised anxiety syndrome, panic anxiety and obsessive–compulsive syndrome.

We have previously followed a number of women with depression and anxiety during pregnancy as well as a random sample of women who felt well during their pregnancy. The women were followed up six months after delivery through telephone interviews in order to confirm diagnoses of anxiety and/or depression. Although the study was not designed to show how frequently anxiety syndrome or depression occurs, we found a significantly higher incidence of more severe anxiety syndromes and more severe depressive disorders in the postpartum period than during pregnancy. During pregnancy mild depression was fairly common, but this diagnosis became relatively less common in the postpartum period. Of the women who were followed up, a larger number were entirely well in the postpartum period, but those women who were diagnosed during this period were significantly sicker and more affected than the pregnant group had been (Andersson 2006).

Postpartum depression includes any depression that occurs in the first year after childbirth. It is, however, most common in the early part of this period, as early as three months after delivery. Postpartum depression can be just as pronounced as major depression, but is often reported to have a high recovery rate and a

shorter course. However, depression during this period has a major impact on the bonding process between the woman and her newborn child, and can have lasting effects on the child's development. Several potential explanations for postpartum depression have been proposed. Risk factors include socioeconomic factors, a history of depression, poor support after childbirth and disturbed sleep. We have also been able to show an association between postpartum depression and the time of year when the child was born. Women who give birth during the last three months of autumn are clearly more vulnerable, irrespective of whether the depression occurs relatively soon after delivery or not until six months later (Skalkidou 2009). There are also genetic and hormonal vulnerability factors for developing postpartum depression, and we have shown that women with certain genes linked to the serotonin system and to the noradrenaline system are at higher risk of depression. Another possible biological factor which has been discussed is sensitivity to the big changes in steroid hormone levels seen during late pregnancy and delivery. Earlier studies on animals and humans have suggested that large changes, for instance in progesterone levels, can trigger anxiety symptoms. Women with severe premenstrual complaints, who in other contexts react to hormonal changes with symptoms of anxiety and depression, are an at-risk group for developing postpartum depression. Another biological factor which raises the risk are the profound changes in the body's stress regulation that occur during pregnancy.

To clarify the biological effects of pregnancy and delivery and the hormonal systems involved, and to describe how postpartum depression arises and develops, we recently initiated a study with a clear focus on measurable biological variables. The study will focus on women who have no history of depression, whose first experience of it occurs during the postpartum period. Postpartum depression probably arises in different ways in women who are experiencing depression for the first time and in those who have a history of psychiatric vulnerability.

Hormones, women and the brain

We have worked with various models to clarify the effects of our female sex hormones on different areas of the brain's functions and on neurotransmitter systems in the central nervous system (CNS). We are also working with functional magnetic resonance imaging, but will not be presenting data from those studies in this review.

To obtain insight into how the female sex hormones oestrogen and progesterone influence the above functions, we are using experimental models which can be applied in animal experiments as well as in humans. This offers us the advantage of using preclinical research to clearly identify which areas of the brain and neurotransmitter systems are influenced, which at least gives us an estimate of how oestrogen and progesterone affect the CNS in women.

One animal model which finds application both in animals and humans is the startle response'. The startle response is the blink reflex triggered by a sudden loud noise or when something is waved right in front of one's face. Variation in the blink reflex is mediated, in part, by the amygdala nucleus in the brain. This evolutionarily ancient area of the brain is involved in the perception of fear and anxiety (Lang 1990). Injury to the amygdala leads to an inability to react with fear or anxiety, while increased amygdala activity is found in individuals with phobias and other anxiety disorders. Earlier studies have also shown that progesterone taken in tablet form leads to increased amygdala activation in healthy women with no premenstrual complaints.

The startle response can be influenced in various ways. In a trial subject, it can be increased by exposure to unpleasant impressions, shock or the threat of a shock. This is called affective modulation of the startle response. The blink reflex can also be inhibited by a less pronounced noise impulse given before the reflex-triggering noise, as a warning. This is called prepulse inhibition and reflects the brain's ability to inhibit incoming sensory messages. Both the affect-modulated and the prepulse-inhibited startle response are influenced by sex hormones and the reproductive state.

The affect-modulated acoustic startle response (ASR) is used to examine the degree to which an individual's blink reflex can be influenced by viewing unpleasant and pleasant images, and an effect on the blink reflex in expectation of the charged images can also be demonstrated. Increased affect modulation of the startle response is found in patients with a specific phobia, while depressed patients demonstrate reduced affect modulation. Patients with anxiety syndrome have a higher baseline startle response, but less pronounced affect-modulation.

We have shown that women with severe premenstrual complaints have an increased affect-modulated startle response on the days before menstruation (the luteal phase), but this does not apply to the period before ovulation. While this could reflect increased amygdala activation (and other important brain areas involved in depression/anxiety) in patients with severe premenstrual complaints during the luteal phase of the menstrual cycle, further studies are clearly needed to confirm the data. We also have preliminary findings indicating that affect modulation is changed during pregnancy and after delivery. Healthy women in the postpartum period show reduced affect modulation compared to healthy pregnant women, which in practice means that changes seen after childbirth are closer to the reaction seen in depressed women. This could be explained by the impulse-inhibiting effect of the breast-feeding hormone oxytocin on the amygdala. We are currently investigating whether a change in affect modulation during pregnancy and the postpartum period is associated with an increased risk of postpartum depression.

Prepulse inhibition of the startle response (PPI) is measured by investigating how the trial subject's startle response is inhibited by hearing a weaker warning sound 100 milliseconds before a reflex-triggering sound pulse (Geyer and Braff 1987). PPI is a measure of the brain's ability to filter incoming sensory messages and is considered to be linked to concentration ability. Patients with schizophrenia have reduced prepulse inhibition, and influences on PPI include the dopamine system and amygdala activity. Besides the

link to mental disorders, reduced prepulse inhibition is also found in patients with most anxiety syndromes.

What makes PPI especially interesting from a reproduction perspective is that women have a lower PPI than men, and also that in women the PPI varies with oestrogen and progesterone level. Our research group has previously shown that high hormone levels in the final stage of pregnancy are associated with a reduced PPI, while low hormone levels in postmenopausal women lead to a normalisation of PPI. In these women, PPI normalisation is seen primarily in those who have naturally low oestrogen concentrations; normalisation does not occur in women who have fertile oestrogen concentrations, either because of obesity or because they are taking oestrogen in some form. Women who report adverse mood effects of combined oral contraceptives have reduced PPI, as do patients with severe premenstrual complaints, but only in the second phase of the menstrual cycle, i.e. after ovulation. It thus appears that in some women oral contraceptives can lead to changes resembling those we see in women who react to their own menstrual cycle.

We also find in our studies that women with severe premenstrual complaints who have particularly pronounced anxiety symptoms during the menstrual cycle in which we are investigating them have a more pronounced PPI. Since PPI is influenced by both hormones and anxiety symptoms in women, this becomes an important variable to investigate if one wants to build up a picture of which women of fertile age are particularly vulnerable to mental ill health.

Does mental ill health affect reproduction in women?

Depression and pregnancy have interested many researchers. It has been postulated that depression itself could have consequences for pregnancy outcome and fetal well-being. American studies have shown that depression during pregnancy may be linked to an increased risk of early or premature delivery, which in turn is associated with a higher risk of permanent injuries to the child. However, American studies in this field are difficult to assess since they primarily deal with high-risk cohorts such as black populations

in poor areas and inner-city populations. Concurrent alcohol and drug abuse probably contributes to the higher risk of serious complications in the child, reinforced not least by an inequitable healthcare system and generally (from a Western perspective) relatively poor childbirth and pregnancy statistics. USA has twice the incidence of premature births compared to Sweden and Western Europe. In our Swedish, population-based studies of pregnant women we find anxiety and depression occurring in 14 per cent of women in mid-pregnancy. Mild depression and anxiety are most common, while major or endogenous depression is seen only in about 4 per cent of the mothers-to-be. In Sweden, where we have good access to free maternal care, we do not see increased morbidity associated with delivery or an increased incidence of premature deliveries. On the other hand it seems that pregnant women with anxiety or depression are more likely to undergo caesarean section, seek healthcare more often, are on sick leave more often and suffer to a greater extent from pregnancy-related complaints such as nausea and abdominal pain (Andersson 2004).

Mental ill health can impact a woman's fertility. Chronic stress, eating disorders and severe depression can all cause a woman to lose her menstruation and become infertile. It is likely that other psychiatric problems also affect fertility, but more subtle influences are harder to measure. One way to investigate the effect of mental ill health on fertility is to look at couples who seek treatment for involuntary childlessness. Here pregnancy outcome after in vitro fertilisation can be used as a measure of the effect of mental health on fertility. Another measure which also reflects the influence of mental ill health on fertility is if depression and/or anxiety disorders are over-represented among couples in whom we can find no reason for the childlessness, i.e. what is called unexplained infertility.

Involuntary infertility affects about 15 per cent of all couples of fertile age in Sweden. In about one-third of cases the diagnosis is female factor infertility, in one-third male factor infertility, and in one-third the diagnosis is unexplained infertility. In vitro fertilisation, IVF, is today the most common treatment for all types of infertility.

IVF treatment is demanding and involves stress, anxiety, expectations and disappointments. A treatment cycle lasts about six weeks and includes a hormonal down-regulation phase, hormone stimulation for follicular development, ovarian puncture with ovum retrieval, fertilisation of the ova, reintroduction of a fertilised ovum and then waiting for the pregnancy test. One in three women becomes pregnant and one in four gives birth after IVF treatment. In 2001 over 8,000 IVF treatments were initiated in Sweden and 33 per cent resulted in clinical pregnancy. About 2,500 children are born in Sweden each year as a result of IVF, representing 2.5–3 per cent of all children born. About 55 per cent of couples who complete all three IVF treatments will give birth to children.

Involuntary childlessness must be regarded as a life crisis; it can be mentally stressful and have a negative impact on the couple's life situation. That mental health is affected by the agitation, anxiety and depression associated with IVF treatment has been documented in several studies. On the other hand we know little about how mental ill health influences pregnancy outcome in IVF treatment, and how this in turn relates to childlessness. Earlier studies have shown that men and women have similar emotional reactions during IVF treatment, and that the most stressful element is waiting for the result of the pregnancy test. Women who had been anxious or depressed before the treatment were less likely to complete all the IVF treatments.

We have investigated how often depression and anxiety disorders occur in couples with involuntary childlessness, both women and men, who are starting IVF treatment. About one-third of women who underwent IVF treatment had an anxiety or depressive disorder while the corresponding figure for men was around ten per cent. These figures are higher than those found in studies of the general population and probably reflect the fact that the cohort we studied was suffering the strain of an infertility crisis and was undergoing a demanding treatment. An increased risk of depression is seen in women whose pregnancy test was negative, whereas the men were entirely unaffected by the treatment outcome. Anxiety disorders

were not at all affected by the pregnancy outcome, which probably reflects the worry that can be experienced even by women early on in pregnancy after assisted fertilisation. Men with unexplained infertility were more depressed than men who had other infertility diagnoses (Volgsten 2008).

Nor does a positive outcome of IVF treatment provide a cure for symptoms of depression. About one in five women remain depressed even if their treatment results in pregnancy (Volgsten 2008). We also find that women with the most pronounced neurotic personality traits have greater difficulty in becoming pregnant during IVF treatment. Earlier studies have shown differing results, but those studies have primarily focused on depressive symptoms without evaluating clinical diagnoses.

The future

Depression is predicted to become one of the world's leading health problems in the future, and is one which affects women to a greater extent. Some data indicate that the incidence of depressive symptoms has increased over time among young women in Sweden, and the prescription of antidepressants to women between 20 and 24 years of age has risen markedly since the year 2000. While there are a great number of models to explain why women are affected to such a high degree, it must also be pointed out that there are differences in how vulnerability factors are manifested in men and women, and that these differences in turn may relate to the female sex hormones. As can be seen from this chapter, there are major knowledge gaps to fill regarding the influence of sex hormones and reproductive events on mental health in women.



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Maternal mortality in Sweden – comprehending the incomprehensible refusal to accept acute caesarean section

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- Why do immigrant women from low-income countries have a sceptical attitude towards surgical interventions such as caesarean section?
- Why is it that, despite this sceptical attitude, they make up a large proportion of those who undergo acute caesarean section, at the same time as running a greater risk of death than other ethnic groups?
- How is it that physicians and midwives, despite having experience of patients who refuse caesarean section, have not investigated the reasons behind this?
- What can Swedish obstetric care workers do to address the problem?

Our studies deal with these issues and the encounter between healthcare workers and women from low-resource countries who are giving birth.

In Western countries, African women are over-represented in terms of maternal mortality as well as perinatal and neonatal mortality (i.e. death of the child during or after delivery). They are also at higher risk of undergoing caesarean section, even after background factors and obstetric risk factors (i.e. risks associated with the pregnancy and childbirth) have been taken into account. At the same time, we know from various interview studies that there is widespread fear of caesarean section among African women exiled in the Western world. This phenomenon has been observed since the early 1990s in women from the Horn of Africa who have emigrated to Europe or North America. A study of deaths associated with delivery (perinatal deaths) in Sweden found ‘refused caesarean section despite medical indications’ to be one of the most frequent causes of perinatal death in children of East African women compared to children of Swedish women. A characteristic of this group, particularly the Somali patients, is that they see no benefit in acute caesarean section despite signs of serious symptoms such as vaginal bleeding or impending fetal oxygen deficiency.

Paradoxical associations

The 2001 UK report ‘The National Sentinel Caesarean Section Audit’ found the incidence of caesarean section to be highest in the ‘Black African’ ethnic group (English designation; corresponds to ‘Africans south of the Sahara’ in Swedish statistics) after adjusting for factors such as age, previous caesarean section, duration of pregnancy, presentation of the child and birthweight. This group had a higher rate of surgery for impending oxygen deficiency than other ethnic groups. A later report from 2004 showed a continuing pattern. Acute caesarean section was twice as common among ‘Black Africans’ (21%) as among ‘White women’ (English designation; corresponds to ‘Western Europeans’ in Swedish statistics) (11%). This is a remarkable ratio, since qualitative research involving interviews with Somali women in maternity wards clearly shows widespread resistance and often strong fear precisely about caesarean section. A paradox emerges when the high incidence of acute

caesarean section and mortality in this group is Birgitta Essén, Sara Johnsdotter and Paula Binder studied against the knowledge that women say that they do not wish to undergo caesarean section.

Our research also involves interviews with healthcare workers (obstetricians and midwives) from different ethnic groups who have extensive experience of meeting women from various countries who are giving birth. The results show that healthcare workers have been aware for quite some time that immigrants from African low-income countries in general, and Somalia in particular, are afraid of caesarean sections. Many of those we interviewed told us about difficult situations they had faced, where for instance they were unable to convince either the mother or the father of the benefits of undergoing acute section in order to save the child.

And yet this knowledge has not led to any professional solutions or clinical guidelines in the way that a purely medical problem generally does. Nor have midwives set up counselling of the type offered to women who are afraid of normal vaginal delivery. A social anthropological approach may explain the paradox of this high incidence of caesarean section in a group that evidently does not want caesarean section.

Explanatory model

What happens in the hospital that leads to so many Somali women being at risk for acute caesarean section – even though many of them feel this strong resistance, and not infrequently express it?

One explanation may be that sociocultural causes of medical problems are not defined by the medical profession, but are handled on the basis that each individual handles them to the best of their ability and going partly on ‘feel’. This also means that the stimulus for obstetricians to solve the problem is not the same as it would be if the underlying causes were more purely medical. A situation where the patient refuses a life-saving intervention is interpreted by the obstetric staff as showing a fundamentally different attitude, a phenomenon which is cultural and therefore unchangeable, and so little interest is generated in finding a disease description or remedy

for the patient's 'strange' ways. And so the profession leaves this problem to the foreign-born patient, since she does not 'understand' medical interventions that to us are good and well defined. It ceases to be a medical matter and is regarded instead as the patient's private affair. Since the doctor and the midwife lack knowledge as to why Somali women are negative about caesarean section, nothing changes, as we can see from the statistics.

One of our studies in British Somali women reveals how not going to the labour ward 'in time' can be perceived as a good strategy for avoiding caesarean section. The thinking is that if contractions are fully established, it will be too late for the doctor to operate. Late arrival is seen as a way of avoiding the risk of acute caesarean section:

When I had my second baby I did not agree with them. Why I'm saying this is, because if they wouldn't have told me that I had so many problems, that actually was not correct as I gave birth to a healthy baby, I would just have stayed at home and got a normal labour pain and then go to the hospital (Somali mother in London)

This Somali woman saw no benefits from caesarean section despite an imminent threat of fetal oxygen deficiency:

*I had caesarean sections with my first and second child and the advice I give my friends is: Don't go to the hospital early – wait. When they got going and were about to section me, my waters broke and the child came out (and was healthy). What did I tell you? Don't go to the hospital early! Wait!
I: What happened then? Can't it be dangerous?
The interpreter translates: They lie (the doctors)! They say they want to section people because the heart isn't beating, but when the child comes out the heart is working as it should. They lie all the time. (Somali woman in London with a Swedish interpreter; this is the only interview cited that has been translated out of the Swedish – in the others, the original English is reproduced.)*

Another woman describes how she perceived her strategy as successful:

I told them, the doctor, that I still wanted to deliver naturally. In Somalia they do that even if it is a breech presentation ... Then they told me that before I get the contractions that I should come in to the hospital but I didn't want to because I knew they were going to do a caesarean section on me so I waited until I had the contractions and was open five centimetres. Then, I went to the hospital.

Why do Somali women refuse caesarean section?

To best handle this clinical situation with women who suddenly refuse caesarean section, we need to develop anthropological theories that will give us a deeper understanding from the inside of what the Somali women are basing their strategy on.

Immigrant women's experience from very poor home countries is that caesarean section is associated with life-threatening complications for both the mother and the child. Maternal death is a reality for many immigrant women, as it is not, or not at all in the same way, for Swedish women or the staff working in Swedish labour wards. One woman describes her immediate thoughts when the doctor said they would have to give her a caesarean section:

First I was shocked, I will not survive I thought immediately. Then the doctor talked to me, telling me that it was not dangerous and that I would survive. I did not understand everything and I felt that I had no choice. I was thinking of women in Somalia who did not survive.

In several African countries it is customary for the mother to bid farewell to her family before setting off to give birth. There is a proverb saying that 'the pregnant woman travels the road between life and death'. The background to differences in the perception of delivery is often related to the fact that women who refuse caesarean section come from very poor countries with high maternal and infant

mortality compared to Sweden. When doctors encounter Swedish women who demand caesarean section, they do not always reflect on sociocultural traditions since they belong to the same culture. Somali patients, by contrast, are thinking about risk, with strategies for avoiding or refusing caesarean section that are often rational but based on an entirely different obstetric reality from what we are used to. Fear of caesarean section therefore has more to do with socioeconomics and poverty than with culture as such. Other traditions and different explanatory models among patients can therefore contribute to obstetric catastrophes (statistically expressed in terms of higher maternal and infant mortality) if they are not identified and defined in time, or if the mother does not realise the benefit of changing her ways in her new home environment.

Clinical advice to healthcare staff

The most constructive approach may be to work to ensure that the confused situation in the delivery room where decisions about acute caesarean section are taken does not need to arise. Pregnancy check-ups at the maternity clinic offer a good opportunity to raise the issue. Here there is room for everyone's voice to be heard. The women can be clearly informed about the medical indications for caesarean section and other labour-inducing interventions, and about the safety of the interventions in Sweden compared to their home country. In the delivery room the patient's ideas about caesarean section should be discussed before a potentially acute situation arises.

It has been postulated that sexual mutilation and lack of knowledge about circumcised women could lead to more caesarean sections. In our extensive material we found that neither healthcare staff nor the Somali women considered circumcision as such to be a problem during delivery. In Sweden, extensive educational efforts have been made since the mid-1990s. Many midwives and physicians in Sweden nowadays have a fairly broad experience of meeting patients from different countries. Today's students in various healthcare disciplines are often given basic knowledge about the circumcision question.

A circumcision scar in the vulva is not an indication for caesarean section. The mouth of the vagina, perineum and vagina itself are never the object of traditional interventions. However, sexual mutilation is not a standardised operation but a trauma which may have taken place under unsanitary conditions with a broad range of after-effects for the individual. The simple technique of opening an existing circumcision scar (defibulation), i.e. dividing the skin bridge that often extends between the labia, can be learned and performed at any time during the pregnancy or delivery, ideally under local anaesthesia.

The anamnesis, or medical history taking, is a fundamental instrument for making a correct diagnosis and preventing medical complications, misunderstandings and unnecessary interventions. Using an interpreter (directly or by telephone) is often the only way to communicate with patients who are not native speakers of Swedish. This is a cost-effective way to increase patient safety and contributes to ensuring that the work is carried out in accordance with the Health and Medical Services Act, which requires care provision to be carried out in consensus between the care recipient and care provider. Specialised ‘cultural interpreters’ exist who, in addition to simply translating the language, act as ‘bridge builders’ between care providers and care recipients. A cultural interpreter can bring out the medical problems she knows the doctor considers relevant. What the woman says during her appointment with the doctor – her account of her physical condition in the framework of her overall life situation – is considered subordinate to her obstetric anomalies, which can be dealt with by examinations of a technological nature. Here the cultural interpreter’s task is to convey this picture to the care provider, in other words convey information which is based on the woman’s experiences in her homeland. At the same time the cultural interpreter will explain the benefits of caesarean section and its low risk in Sweden compared with the woman’s homeland. Medical information about risks is placed in the right context by the cultural interpreter, so that both care recipient and care provider are satisfied. Advice and medical

explanations are translated in a ‘culturally sensitive’ manner so that they are perceived as meaningful by the patient, thus increasing the woman’s compliance with the doctor’s instructions. This allows medical decisions involving the woman’s whole life situation, earlier experiences and unique circumstances to be made in a better way.

It should be emphasised that this is not a question of adapting obstetric treatment modalities for every ethnic group. Neither is it a question of whether some cultures are more accepting of maternal and child mortality. Whether the question is one of ‘demanding’ or of ‘refusing’ caesarean section, it is often the case that the patient is choosing the strategy that she considers safest for herself and the fetus – a choice which may be at variance with the obstetrician’s strategies. Whether as care providers or care recipients, we act on the basis of culture-specific perceptions and patterns; but what is seen as ‘the right behaviour’ in the woman’s homeland does not always turn out well in Sweden. But cultural concepts are not static; they can be changed. Instead of arguing about interpretative priority, we should be discussing the patient’s ideas about how best to achieve an uncomplicated and safe delivery: that is, with give and take between ‘the two experts in the room’ – the doctor and the patient.

The clinical advice can also serve to promote knowledge among midwives and doctors: a reminder that not all who approach the healthcare system have the same past experience. With this insight – combined with an approach based on the recognition that every individual has a unique background and life situation – conditions can be created for a more exploratory approach to maternity care consultations with Somali women in the maternal and obstetric care system. This may ultimately create the confidence in the healthcare system which many Somali women currently lack. An expanded consultation of the type described can also contribute to making optimal obstetric care more accessible. Simply to accept that Somali women today suffer more complications than other groups in society is untenable.

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Life situation of women with breast cancer

– management, quality of life and survival

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More and more women in Sweden are diagnosed with breast cancer. Improved diagnostic and treatment methods allow the majority of patients to be cured and live a long life. It is therefore important to learn more about the life situation of women both during and after treatment for breast cancer. New knowledge will enable us to provide care based on a woman's individual circumstances and needs.

The goal of the project 'Breast cancer: management, quality of life and survival. A multidisciplinary project based on a 'breast cancer quality register' is to identify areas that can be improved and are significant for quality of life, return to work, treatment compliance and survival.

With over 7,000 new cases every year, breast cancer is by far the most common cancer among women in Sweden. It is estimated that one woman in ten will develop the disease at some point in her life. The risk of contracting breast cancer increases with age and is highest in the 60- to 69-year-old group. With improved diagnostic and treatment methods, survival has increased considerably in the last forty years, and about 80 per cent of women are now alive ten years after diagnosis. In Sweden there are currently over 80,000 women who have survived breast cancer, the majority having completed their treatment many years ago and being regarded as cured.

In Sweden, the number of new cases of breast cancer has been going up every year since the 1960s. Reasons for the increase include an ageing population, improved diagnostic methods and the introduction of screening. Breast cancer is diagnosed using the ‘triple diagnosis’ method, which involves clinical examination, mammography and tissue samples. Mammography screening is especially important for early detection and has gradually been introduced throughout the country since 1986. As a result, more and more breast tumours are being detected at a favourable stage, which contributes to the fact that for many women the prognosis is good. Among women diagnosed with new (so-called primary) breast cancer, the tumour is most often limited to the breast, in which case the ten-year survival rate is 70–100 per cent. If there is limited spread to axillary lymph nodes, the prognosis is still fairly good, whereas involvement of six or more lymph nodes carries a poorer prognosis. In about 3–4 per cent of women, the cancer has already spread to other parts of the body at the time of diagnosis, and the disease is no longer curable. Although the long-term prognosis is poor, advances in medical treatment allow many of these women to live with their breast cancer for many years.

Care and treatment

Breast cancer care is based among other things on national guidelines as well as national and regional care programmes. These documents contain recommendations intended to ensure that all patients have access to efficient and equitable care based on scientific Claudia Lampic, Marie Höyer and Mats Lambe knowledge and proven practice ('evidence-based'). Breast cancer care is a multiprofessional undertaking in which different professional groups collaborate: radiologists, pathologists, breast and plastic surgeons, oncologists, breast care nurses, social workers and others. It includes diagnostic work-up, surgery, medical treatment, follow-up, nursing care and rehabilitation.

In almost every case, treatment starts with surgery to remove parts of the breast, or in some cases the entire breast. When a woman receives her breast cancer diagnosis, the goal is for surgery to take place within three weeks. Any breast reconstruction generally takes place after treatment is completed, but can also be performed in direct conjunction with the operation. After surgery, most women receive some form of adjuvant therapy intended to kill any remaining cancer cells and thereby reduce the risk of a recurrence.

The most common adjuvant therapy is radiation, which is generally administered as short daily doses of radiation over five weeks. When necessary, chemotherapy is given in repeated treatment cycles at a few weeks' interval. In addition to this are antibody and hormonal therapy, often given for up to one and up to five years, respectively. Which treatment is given depends on factors such as tumour spread at the time of diagnosis and the characteristics of the tumour. In breast cancer, the risk of recurrence is greatest during the first three years after diagnosis. During the first year, all breast cancer patients are called for a follow-up visit with mammography. The National Board of Health and Welfare recommends a structured follow-up period of five years.

Nursing care and rehabilitation. A cancer diagnosis often means a major readjustment for the individual woman. While many cope well with the mental strain, strong psychological reactions are quite usual. In addition, the surgical and other oncological treatment may cause physical complaints that can have a negative impact on daily activities, including the ability to work. Communication and coordination are therefore important parts of cancer care and are indispensable for creating a sense of security. At appointments with doctors and breast care nurses, the women receive information about their treatment as well as practical help with any adverse effects or complications. Where indicated, it is also important to be able to offer contact for instance with a physiotherapist, social worker, psychologist, chaplain or dietician. Rehabilitation after completion of treatment aims to reduce the physical, mental, social and existential consequences of diagnosis and treatment. At several places in Sweden there are special units for psychosocial cancer care where information, practical assistance, emotional support and other services are provided to women who need help readjusting to everyday life.

Quality of care. The National Board of Health and Welfare has been tasked with creating quality assurance in breast cancer care by developing national guidelines for care and treatment. The guidelines include outcome measures as indicators of quality in the healthcare system. Traditional outcome measures of good care and treatment have been disease-free survival and total survival. However, the importance of evaluating the healthcare system on the basis of other measures is being increasingly emphasised. Nursing care, the attitude of care staff, and psychosocial management are now considered necessary components of good cancer care. The Government enquiry ‘A National Cancer Strategy for the Future’ (SOU 2009:11) notes the lack of reliable data about patient perceptions of quality of care, the attitude of care staff, and adaptability to individual patient needs. To strengthen follow-up and evaluation of cancer care from a patient perspective, the enquiry recommends among other things

that measures of the patient's health-related quality of life and care satisfaction be introduced into the national quality registers in cancer care.

Studies in other countries have shown that information, staff attitude, continuity and accessibility are important aspects of care satisfaction among breast cancer patients. Despite the generally high level of satisfaction in these areas, there is also considerable room for improvement. So far as Swedish cancer care is concerned, lack of continuity and long waiting times, among other things, have come in for criticism. However, Swedish research on care satisfaction among cancer patients in general and breast cancer patients in particular is limited. Organisational and societal differences limit the extent to which results from international research can be extrapolated to Swedish conditions. Another deficiency is that care satisfaction is often measured using questionnaires that are general and provide limited insight into how women with breast cancer experience different parts or phases of their treatment. Detailed studies of patient satisfaction are therefore necessary in order to identify areas within breast cancer care that need to be improved.

Another important question is whether the patients' care experiences have significance for their general well-being. Several studies have reported that dissatisfaction with breast cancer care is associated with a poorer quality of life and more pronounced symptoms of anxiety and depression. These associations can be interpreted in two different ways, both of them significant for the provision of cancer care. One interpretation suggests that it is women with a poorer quality of life and more anxiety and depressive symptoms who are dissatisfied with the care. This highlights the importance of identifying women who feel unwell in order to offer them extra support measures. The alternative interpretation, which is that dissatisfaction with care contributes to a poorer quality of life and more emotional problems, highlights the importance of identifying parts of the care which need to be improved.

Life situation during ongoing treatment

Quality of life. How is a woman's life situation and perceived quality of life affected when she develops breast cancer? Within cancer research the concept of 'health-related quality of life' is often used. This usually includes assessment of various disease symptoms, adverse treatment effects and the individual's functional status. 'Functional status' means ability to function in daily life in terms of physical function (e.g. general condition), emotional function (e.g. mood), role function (e.g. social responsibility) and social function (e.g. personal relations). It is also believed that personal perceptions of quality of life are influenced by biological and physiological variables (such as disease severity), individual factors (such as age) and environment-related factors (such as social support).

Research shows that women undergoing treatment for breast cancer generally experience a poorer health-related quality of life compared to healthy women. Frequently reported problems include the woman's role function and social functioning as well as symptoms such as persistent fatigue, sleep disturbances and pain. In addition, the women themselves often give their health and quality of life a low score.

Anxiety and depression. Anxiety and depression have a major impact on the breast cancer patient's life situation, physical health and health-related quality of life. Research suggests that depression is linked to increased morbidity and also may have a negative effect on the cancer prognosis. Some 20–30 per cent of all breast cancer patients develop anxiety and/or depressive symptoms; the times around the start and end of treatment seem to be particularly stressful. It is therefore important to identify these women in order to offer the best possible medical and/or psychological therapy.

Sick leave and working ability. Sick leave is considered part of the treatment. The National Board of Health and Welfare has developed guidelines for sick leave, but recommends individual assessment of the patient's ability to carry out specific job tasks. While most

women retain their ability to work before an impending breast cancer operation, some develop serious psychological problems that prevent them from working both during and after the operation. Although the surgery can cause pain and tightness in the operated area, the effect on physical function is usually limited. It is therefore recommended that sick leave be limited to three weeks after surgery. In women who have had lymph nodes surgically removed and whose job tasks involve heavy arm strain, six weeks' sick leave may be justified. Surgical removal of axillary lymph nodes can also cause lasting injury leading for instance to swelling, ache and reduced mobility in the affected arm.

Although ability to work is often good in women who undergo radiation therapy, the treatment can cause symptoms such as burning and pain towards the end of the treatment period. Many patients also complain of pronounced fatigue. Some women have to travel a long distance to the hospital where the radiation therapy is given, and practical issues often arise which affect their ability to work during the treatment period. Chemotherapy can cause fatigue as well as other adverse effects (such as nausea, muscle pain and increased susceptibility to infection) that affect the ability to work, and sick leave during chemotherapy is therefore regarded as justified. Women can regain their working ability between treatments, so part-time work can be a good solution. For both chemotherapy and radiation therapy, the National Board of Health and Welfare has made the assessment that it takes women one to two months to regain function and ability to work. Hormonal therapy can cause symptoms such as hot flushes and sweating, but does not in principle justify sick leave. There may nevertheless be a negative effect on the ability to sleep at night. Psychological reactions can also arise and affect the ability to function. In metastatic breast cancer, the woman's physical function is often impaired as a result of pain, fatigue and adverse effects of treatment. In many women the psychological impact of living with incurable cancer also contributes to a reduced working ability. However, some patients in this group may periodically regain their normal function and thus also their ability to work.

Life situation after treatment

Quality of life, anxiety and depression. As a group, women treated for breast cancer in the long term appear to have as good a quality of life as women who have not had breast cancer. While most breast cancer survivors thus regain a good quality of life, there is also evidence that many have residual problems relating for instance to physical and sexual function. Problems with anxiety and depressive symptoms may also persist for several years and frequently remain even when the woman has been cured. Raising the level of knowledge about problems that can arise or persist long after treatment is therefore important in order to be able to work with targeted measures.

Sick leave, working ability and return to work. Most women of working age who have been cured of their breast cancer return to work. Some however have physical and psychological complaints that persist even after treatment has been completed. According to a report from the National Board of Health and Welfare's Centre for Epidemiology (2003), the average period of sick leave after breast cancer surgery was eleven months. Social scientist Aina Johnsson in her dissertation (2009) recently reported on the rate of sick leave in a group of women ten months after breast cancer surgery. She found that 41 per cent of the women remained on full or partial sick leave after completion of radiation therapy and/or chemotherapy. A large Danish study showed that one in five women still experienced reduced ability to work 5–15 years after breast cancer surgery, while one in ten had given up or changed their job as a result of their complaints.

Why are sick leave periods so much longer than recommended? How could women's working ability and return to work be facilitated after breast cancer treatment? Research has shown that cancer patients in general have a special need for various work-related support measures, both from the healthcare system and in the workplace. Physical and psychological stress at work, the employer's attitude and the opportunity for work training have proven to be very important elements in the rehabilitation process.

Which women are at risk of having a poor quality of life? All healthcare in Sweden should be individually adapted and based on each patient's circumstances and needs. Of special importance is the ability to identify patients at risk of having a poor quality of life in order to offer specially adapted care and perhaps expanded support measures. With regard to women with breast cancer, research points to a number of factors that contribute to a higher risk of poorer health-related quality of life and symptoms of anxiety and depression.

Age and medical factors. Several studies have investigated what significance the woman's age has for quality of life during and after breast cancer treatment. Results indicate that younger women with breast cancer (below age 50) often have a poorer health-related quality of life and more often suffer from anxiety and depressive symptoms than do older women. While younger breast cancer patients may experience more problems of a sexual or financial nature, older patients tend to have more problems for instance with physical function.

Studying the significance of medical factors for quality of life, anxiety and depression is complicated by the difficulty separating consequences of the disease from the effects of treatment. Both the disease stage and the type of medical treatment have been found to relate to quality of life and symptoms of anxiety and depression in women with breast cancer. The question then arises whether a poorer quality of life is due to the woman having more advanced disease or to her having undergone more arduous treatment.

Several studies have also investigated whether the type of surgery has significance for health-related quality of life and the incidence of anxiety and depressive symptoms. Results show that breast-conserving surgery has only a minor effect on women's psychological and social functioning, compared to when the whole breast is removed. Breast reconstruction, on the other hand, has a clearly positive effect on well-being.

If a woman has other diseases in addition to breast cancer, this contributes to a poorer health-related quality of life. An association has also been found between a previous history of psychological problems and subsequent symptoms of anxiety and depression associated with the cancer and cancer treatment.

Data about the woman's age and medical factors related to the disease and treatment are collected routinely in the course of the disease in interviews with the patient and during examinations and operations. The question is whether there are any other factors in addition to these that could help healthcare staff identify women with breast cancer early in the course of their disease who are especially vulnerable and in need of advice and support.

Civil status and social support. Breast cancer is a disease which not only impacts on the woman but also on her family and other close relatives. Relationships, particularly a partner relationship, can play a prominent role and be a significant support to the affected woman. On the other hand, it can happen that family members themselves suffer an emotional crisis which renders them incapable of providing the support the affected woman needs. Studies have shown that more single women than cohabiting or married women with breast cancer report a poorer health-related quality of life as well as more symptoms of anxiety and depression. Lack of social support from family and friends is a risk factor for this.

Socioeconomic factors. Under its principles, Swedish healthcare should be provided equitably according to need; it should be democratically governed and funded by all. A high value is placed on patients' sense of security – something reflected in, among other things, the social insurance system and the funding of the healthcare system, which involves limited user fees. In spite of this, people in Sweden who live in poorer socioeconomic conditions are at greater risk of developing and dying of cancer, and there are signs that social health inequalities may increase in the future (SOU 2009:11).

What then do we know about the significance of socioeconomic factors for health and quality of life in women with breast cancer? In a 2009 knowledge overview on social differences within the healthcare system, the Swedish Association of Local Authorities and Regions (SALAR) points out that low socioeconomic status contributes to poorer survival in breast cancer. Although research in this area is limited, existing findings suggest that lower income, lower education and a lower grade of occupation may be linked to poorer health-related quality of life and more symptoms of anxiety and depression in women with breast cancer.

Which women risk not returning to work? Despite national recommendations and care programmes for breast cancer, there are regional variations and age differences with respect to sick leave periods. According to a report from the National Board of Health and Welfare's Centre for Epidemiology (2003), older women who are treated for breast cancer have fewer sick days on average than younger women. The explanation for this could be that younger women more often undergo more advanced treatment. Another possible explanation is that younger women tend to have a poorer health-related quality of life and experience more anxiety and depressive symptoms, which research has shown can have a negative impact on returning to work.

Several studies have found treatment-related complaints to be the reason why many women do not return to the labour market. In particular, adverse effects such as persistent fatigue and hot flushes limit the women's working ability. Both chemotherapy and hormonal therapy are known to contribute to lengthy sick leave periods even though, according to the National Board of Health and Welfare, sick leave is not generally justified for hormonal therapy. Radical breast surgery results in 50 more sick days on average than a breast-conserving operation.

Although the significance of demographic and socioeconomic factors for work ability and return to work in women with breast cancer has gained increased attention in recent years, the state of knowledge remains very limited. There is some support for the perception that lower income and physically demanding work have a negative effect on return to work.

Compliance with prescribed adjuvant therapy. A major advance in breast cancer care has been the introduction of adjuvant therapy with anti-oestrogen preparations after surgery. The treatment blocks the tumour-growth-stimulating effect of the female sex hormone oestrogen. Five years of therapy with the anti-oestrogen preparation tamoxifen was recommended for about twenty years as standard treatment for women with oestrogen-receptor-positive breast tumours. Controlled clinical studies based on 15 years' follow-up found that the risk of death from breast cancer dropped by 31 per cent if the tumour was oestrogen-receptor-positive and the treatment given for five years. In absolute numbers, this risk reduction represents a 5–10 per cent improvement in long-term survival. However, the effect is dependent on the treatment being given continuously throughout the intended time period.

Knowledge about patient compliance with long-term anti-oestrogen treatment is still limited and no systematic mapping has yet been done in Sweden. Results from international studies indicate that the proportion of breast cancer patients who follow their prescription instructions exactly and complete their treatment is considerably smaller 'in real life' than what is seen in clinical trials where the patient groups tend to be selected. In clinical practice – in other words, out there in the healthcare system – it is estimated that only 50–70 per cent of all patients complete their treatment. Some studies have examined whether, and how, age and geographical region influence compliance. No study has so far looked at the potential significance of social background.

We have previously been able to demonstrate social differences in breast cancer survival in Sweden. Possible explanatory factors

are behavioural (knowledge, values, attitudes, lifestyle, healthcare consumption), social (social support, financial resources) and clinical (diagnostic work-up, type of treatment received, general health status, co-morbidity). More recently, increased attention has been paid to the importance of the individual's personal resources such as knowledge and motivation. No study has yet examined whether compliance with anti-oestrogen treatment varies between breast cancer patients from different social groups.

Our research project

To summarise, earlier research has shown that the majority of women with breast cancer are cured, are satisfied with the care they receive and have a relatively good quality of life both during and after their treatment. There are nevertheless subgroups of women who appear to be at greater risk of negative consequences and who return to work only after a long time, or not at all. Earlier research has identified several factors which appear to be significant for quality of life and the occurrence of anxiety and depression in women with breast cancer. However, it is still unclear how these factors co-vary. Is it, for instance, likely that socioeconomic factors such as poor education and low income could impact the quality of life? In order to investigate the significance of several individual factors for women's quality of life and symptoms of anxiety and depression, they must be studied in one and the same study and in a large cohort of women. As for return to work, there are few studies in this area and much research remains to be done.

An important goal of our research project is therefore to pinpoint the risk factors to which the healthcare system must pay attention in order to identify early those women at risk of a poor disease and/or treatment outcome. Early identification of vulnerable groups or individuals increases the possibility of improving breast cancer care through individually adapted care and support measures intended to prevent problems and improve the life situation for these women.

The Swedish Council for Working Life and Social Research is providing major funding for ‘Breast cancer: management, quality of life and survival. A multidisciplinary project based on a breast cancer quality register’. The project emanates from the Regional Oncology Centre in Uppsala/Örebro Region and the project group includes medical specialists, nurses, psychologists and researchers in epidemiology and psychosocial cancer care. The project aims to:

1. Study quality of life, anxiety and depression in women with breast cancer during and after treatment in order to identify especially vulnerable groups who need extra support.
2. Study the women’s experience of breast cancer care in order to identify aspects of care that can be improved.
3. Study aspects that affect the women’s possibility of returning to work after treatment for breast cancer.
4. Study aspects that can affect the women’s compliance with adjuvant breast cancer therapy and hence their chance of survival.

One of the substudies is entitled ‘Health-related quality of life, care satisfaction and return to work – a prospective long-term follow-up’. This study is based on the Regional Breast Cancer Quality Register in Central Sweden and is being conducted in collaboration with the Regional Oncology Centre in Uppsala/Örebro Region, Uppsala University and Karolinska Institutet.

The study is following a group of about 1,000 women with breast cancer over time, from diagnosis and three years onward. The women will complete questionnaires at three time points during and after their treatment. The final survey in the study will be sent out three years after diagnosis, i.e. during 2010 and 2011.

The questionnaires include questions about care satisfaction, health-related quality of life, anxiety and depressive symptoms as well as working ability and return to work based on established measurement instruments and instruments we ourselves have developed. The study will also include measurement of factors

that have previously been found to be important for quality of life, symptoms of anxiety and depression, and return to work. Data on medical factors concerning the disease and its treatment will be obtained from the regional breast cancer quality register while information on other morbidity, demographic and socioeconomic factors as well as access to social support will be gathered through the questionnaires.

We expect our findings to facilitate identification of women early in their disease who are at risk of suffering negative consequences of their breast cancer. This is an important prerequisite for healthcare workers in their efforts to provide advice and support to patients with special needs. Publication of the first substudy in the project is expected in 2011.

In another substudy we will investigate compliance with prescribed anti-oestrogen treatment in breast cancer patients, focusing especially on possible social differences. Increased knowledge in this area can help reduce inequality in breast cancer survival.

The study is based on data from the Breast Cancer Quality Register in Central Sweden (Regional Oncology Centre in Uppsala/Örebro Region), a social database (LISA, a longitudinal database for education, income and occupation at Statistics Sweden) and the Swedish Prescribed Drug Register (National Board of Health and Welfare). Since July 2005, the latter database registers all drug prescriptions dispensed at the individual level including information on the product (identity, dose, quantity and price).

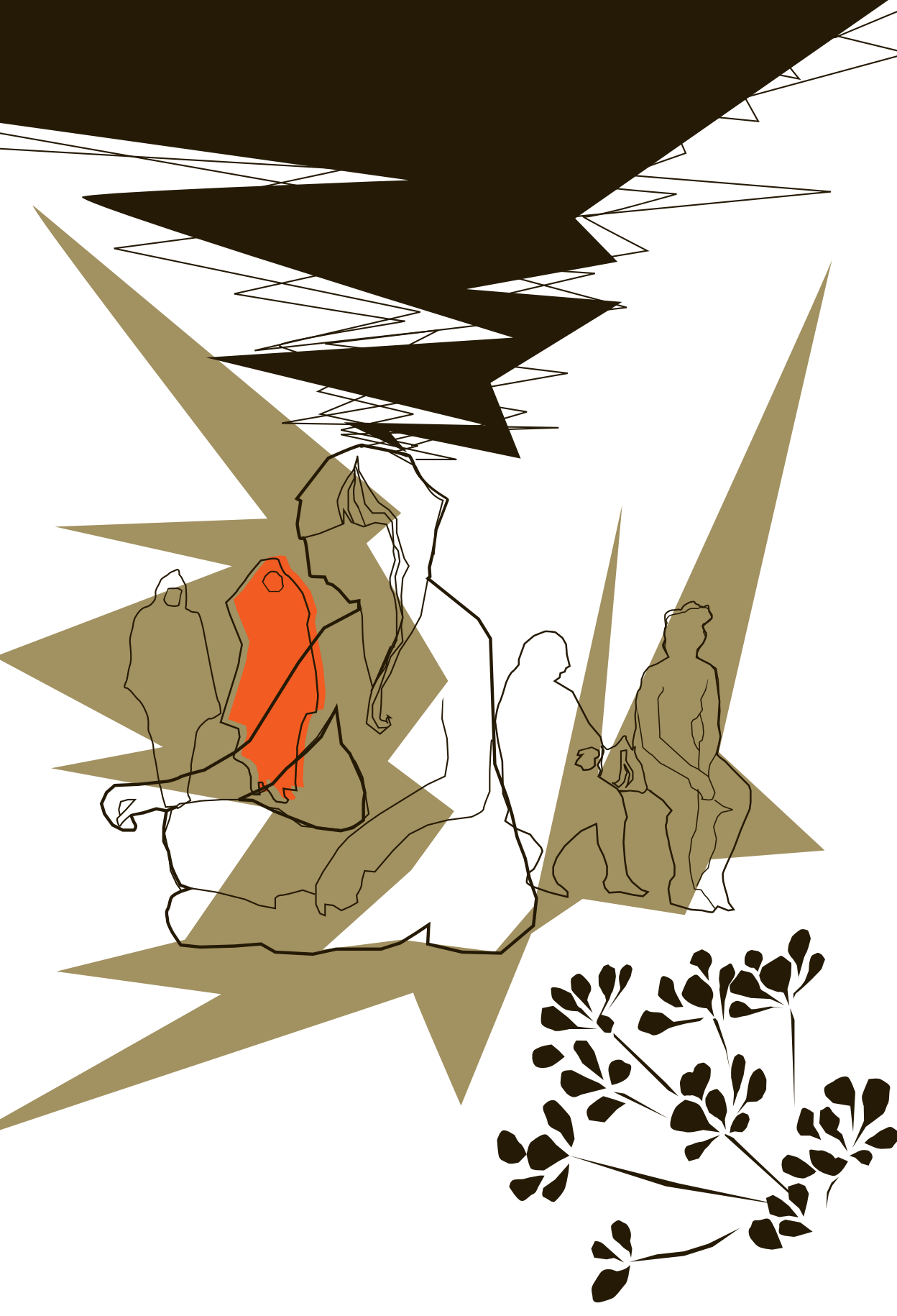
The study cohort comprises more than 4,400 women diagnosed with hormone-receptor-positive breast cancer between 2000 and 2007. According to the breast cancer register, they have been prescribed treatment with tamoxifen and the study will show how many obtain their medication in a quantity sufficient for treatment at the standard dosage. Comparisons will be made between social groups, age and clinical data about the tumour and treatment.

Benefits to the patients, healthcare system and society

Major efforts have been made in Sweden to raise the quality of breast cancer care and ensure that it is equitable. This is reflected for instance in an international perspective by very good survival statistics. There are nevertheless areas with potential for major improvement. This includes aspects of psychosocial management, return to work and compliance with prescribed treatment.

Taken as a whole, the aim of the project is to gather knowledge in order to optimise care and rehabilitation based on every breast cancer patient's circumstances and needs. Results may contribute to more individually adapted care and may benefit not only individual patients, but care chains and society as well. The studies are anchored in existing networks of nurses and doctors, which will facilitate implementation of improvements based on the project's findings.





Mental ill health among refugees and asylum seekers

– differences between men and women

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There is a clear link between mental ill health and high unemployment among foreign-born women. But which is the chicken and which the egg? Do the women find it harder to get jobs because of depression, or is it the unemployment itself that increases the risk of mental ill health? And how can we make a real improvement in mental ill health and unemployment among these women? This is the theme of a research project intended to shape a deeper understanding of mental ill health in refugees and asylum seekers and discuss what we can do about it.

Mental ill health is more common in women than in men, and is particularly high among women from an immigrant background. Unemployment is also high among immigrant women, and the question is: what is the association

between the two? However, the picture has changed over time. When immigration to Sweden increased after the Second World War, for instance, there were periods when more immigrant women had jobs than immigrant men.

They worked as domestic servants, as nurses and in factories.

What do mental ill health and unemployment look like today, and does the answer vary depending on your reason for coming to Sweden – as a refugee, immigrant worker, family member or allowed to stay for humanitarian reasons?

The background to mental ill health may vary (genetic factors, environmental factors and traumatic experiences) in different groups of immigrants. To promote mental health among refugees, perhaps the most vulnerable group, it is important to study what conditions there are given for a life that contributes to good mental health, such as their reception here in Sweden: a factor we can influence.

Some studies show that women refugees do less well than men; others show no difference. Our research indicates that mental ill health in women refugees is not chronic but falls within the spectrum that can be influenced. There is nevertheless a risk that symptoms may become chronic if left untreated and the women continue to live outside society, either as a consequence of being overlooked or because research tends to equate being a female refugee with having mental ill health.

In recent years the present government has stressed what it calls the ‘work approach’ in its refugee policy as elsewhere. In practice this means that newly arrived refugees who have been granted permanent residence in our country are expected to take more responsibility for looking after themselves. This is why it is important that any obstacles inherent in the reception process that make it difficult for foreign-born women – especially refugees – to enter the Swedish labour market should be reviewed and taken seriously.

Different approaches to the problems

There are several ways of illuminating the psychosocial situation of asylum seekers and refugees. Harvey (1996) used a model to demonstrate the impact of an experience such as harassment, war trauma or torture on the individual's quality of life and drew attention to the complex relationship between three factors:

1. Person-specific factors such as age and education.
2. Event-related factors such as violence or trauma and their severity and frequency.
3. The individual's environment.

Antonovsky (1987) in a different model suggested that individuals can cope with severe stress in their life situation provided they are able to experience a 'sense of coherence', something which develops in the course of life. Stress reactions, for instance in the form of mental ill health, can arise when an individual finds he or she has no control over his or her situation. Here the perception of ill health may represent feelings such as inadequacy, lack of hope for the future, exclusion and frustration. A theoretical review (Lindencrona, Ekblad and Johansson Blight, 2006) draws the following conclusions:

- *Each of the four phases of premigration, migration, postmigration and possible return can be stressful for the individual and each phase may present significant threats against a perception of good health.*
- *Migration research suggests that newly arrived refugees often have multiple needs that need to be satisfied through a flexible and sustainable support system with a preventative focus at both the central and local level in the host country.*
- *Health and wellbeing can be positively influenced by the individual gaining more involvement in society and having greater control over his or her life situation.*

Another applicable model for describing environmental influences on mental health is drawn from Silove (1999), who uses the premise of five health systems: attachment, security/safety, identity/role, human rights/justice and existentiality/meaning. The health systems can be illustrated by the following quotations from our meetings with asylum seekers and refugees:

Attachment: ‘I fled as a widow from Iraq to save my children’s future. Now I have lost contact both with my family in my homeland and with my children. Swedish society has taken over their upbringing. My children use bad language which I’m not used to. I feel more and more depressed.’

Security/safety: ‘As an asylum seeker I’m afraid of being deported; I live with people I don’t know in a suburb with lots of immigrants and other socially vulnerable people. I don’t feel secure or welcome and therefore I don’t dare go out.’

Identity/role: ‘Because of the torture and rape, I have no trust in others; I feel unclean and ashamed in front of family members and others around me. My educational background isn’t accepted here and during the introduction my case worker advised me to go back to university after the SFI (Swedish for Immigrants) course and redo my subjects. I find this objectionable, and I and my husband don’t get along at home.’

Human rights: ‘I was discriminated against in my homeland because I had a different religion than the majority population. I often experienced discrimination; for instance, I was forced to stop studying. Now I’m hoping for a future in Sweden.’

Existentiality/meaning: ‘Because of the torture, I’ve lost my belief in any meaning of life. I have started to doubt that there is a God. The long period of idleness as an asylum seeker and uncertainty about the future has reinforced these feelings. I feel empty.’

In other words, the question of mental ill health in refugees and asylum seekers can be studied from various angles. In this chapter we will touch on the following issues:

- Are there differences in health between various immigrant groups, and is the situation different for women and men?
- How are we to interpret the association between mental ill health and unemployment in immigrant women?
- How can the efforts to address mental ill health in refugees and asylum seekers be materially improved, from the general to the specific?

Facts about immigration to Sweden

Statistics Sweden defines a person of foreign background as having been born abroad or born in Sweden of two foreign-born parents. In 2009 the proportion born abroad was 14 per cent. The proportion of foreign-born persons has doubled since the early 1970s. Persons of foreign background in Sweden are a very heterogeneous group. Since the late 1970s, immigrants to Sweden have mainly consisted of refugees, while the group of immigrant workers has been small. The largest group consists of 173,000 persons born in Finland, followed by 117,000 born in Iraq. In addition there are 390,000 persons born in Sweden of two foreign-born parents. Together with the foreign-born group, they represented nearly 19 per cent of Sweden's population on 31 December 2009.

In 2009, family relationship was the most frequent reason (35%) for immigrating to Sweden (34,082 persons in total). The same year over 11,000 asylum seekers (11%) were granted permanent residence in Sweden (including about 1,900 quota refugees). In 2009, the largest groups of asylum seekers were Somalis (24%), Iraqis (9%) and Afghans (7%). In 2009 the Swedish Migration Board granted residence permits to 27 per cent of asylum seekers (98,644 in total). Of these, 20 per cent were refugees, 66 per cent other persons in need of protection while 9 per cent were granted residence permits on grounds of extreme compassion.

Continued on next page.

Facts (continued)

Who is allowed to stay?

Permanent residence permits can be obtained by EU and EEA citizens, persons with a family connection in Sweden (husband/wife or parents in Sweden), persons with another connection to Sweden, persons who have jobs in Sweden (under certain circumstances) and persons seeking protection. For those seeking protection, there are different grounds for residence permits.

Who is a refugee?

Refugees are persons who have been granted a residence permit under the Geneva Convention, i.e. who have good reason to fear persecution and are unable to return to their homeland because of:

- race;
- nationality;
- religious or political views;
- gender;
- sexual orientation;
- belonging to a specific social group.

Who is a person in need of protection?

These are persons who without meeting refugee criteria are in need of protection, in other words persons who have left their homeland and do not want to return there because they:

- have reason to fear for instance a death penalty or torture;
- need protection because of war or other serious turmoil within the country;
- cannot return to their homeland because of an environmental catastrophe.

You can be considered for refugee or protection seeker status in two ways: as a quota refugee, or as an asylum seeker.

Quota refugees

Quota refugees are foreign citizens who before travelling to Sweden have been granted a residence permit under the refugee quota (about 1,900 in 2009) established by Government. Their journey is organised and paid for by the Swedish Migration Board.

Continued on next page.

Facts (continued)

Asylum seekers

Asylum seekers are those who seek asylum at the border or in Sweden, i.e. they apply for a residence permit by claiming refugee or protection seeker status.

Refugees without papers, including hidden refugees

Persons who do not have a residence or work permit or a visa. Individuals without papers are sometimes former asylum seekers whose applications have been rejected but who have chosen to stay by going underground.

Source: www.scb.se and www.migrationsverket.se

Differences in health

Are there health differences between various immigrant groups, and is the situation different for women and men?

Data from Open comparisons 2009 show that health is poorer among those born abroad than in the average population. Much indicates that those in poorest health are foreign-born individuals who have come to Sweden as asylum seekers, refugees or family members of refugees.

Epidemiological studies show that the most common diagnoses among immigrants in the Western world relate to mental ill health and that this applies particularly to refugees. Examples include post-traumatic stress disorder (PTSD) and depression (Fazel et al. 2005). Refugees in high-income countries are about ten times as likely to experience PTSD as the age-matched population. One in twenty suffers from depression and one in twenty-five is affected by generalised anxiety. Besides PTSD and depression, other common psychiatric conditions such as somatisation and alcohol, drug or medication dependence are found in the refugee group. The literature also shows that multiple traumas have a cumulative harmful effect on somatic health.

To understand the different risk of mental ill health in refugees compared to other immigrant groups, it is important to distinguish between pre- and post-migration stress. The former is related to various forms of trauma before the flight, such as war, aggression and torture (Mollica et al. 2001). The second refers to the hardships entailed in moving to a new country, in terms of housing, language and unemployment problems and lack of social attachment (Beiser and Hou, 2001). This also includes loss of status and social belonging and the loss of social networks, culture and language. These two types of stress can each be relevant on their own, but they often co-vary.

A schematic description of the various types of stress is given on the next page.

The fact that refugees have poorer mental health than other immigrant groups, such as immigrant workers, may be explained by their exposure to pre-migration stress, which other immigrants are often spared.

	Refugees	Other immigrant groups
Pre-migration stress	War, aggression or torture trauma	
Post-migration stress	Housing, language and unemployment problems; lack of social attachment	Housing, language and unemployment problems; lack of social attachment

However, not all refugees with traumatic experiences develop PTSD, depression or other psychiatric conditions (Mollica et al. 2001). And even among those who do develop these illnesses, many move on to recovery through self-healing, although it may take several years. It seems, however, that the first two years are critical for normalisation in the host country (Beiser and Hou, 2001). Discrimination, exclusion and social injustice are examples of factors that can be assumed to hinder self-healing. On the other hand, an experience of meaningfulness and access to care resources provide opportunities that may be assumed to result in the individual's choosing a healthy lifestyle when a concrete opportunity to do so occurs. This could for instance apply to someone who is helped to give up smoking. However, this needs to be studied further.

A review of research in this field reveals that the scientific quality of studies of foreign-born individuals is not always good. The most frequent problems are lack of theoretical underpinning, lack of clarity about the questions to be answered, and weaknesses in research methodology (e.g. inadequate attention to transcultural aspects in translations, concepts, scale ratings and norms).

Does mental ill health then differ for female asylum seekers and refugees compared to male asylum seekers and refugees? Some studies, but certainly not all, point to a difference between men and women, with women being at greater risk of mental ill health. One study investigating the prevalence of post-traumatic stress in a cohort of women refugees from Bosnia, for instance, found a high incidence of mental ill health (Sundquist et al. 2005). Is the higher risk of mental ill health in foreign-born women due to war, aggression and torture trauma? We have no way of finding out, since a great deal of criticism has recently been levelled at the processing of women's refugee claims, where it has been shown that women's reasons for seeking asylum are often poorly investigated. There are signs suggesting an increased risk of misuse of tranquillisers and sleeping drugs among women recently arrived from traditionally Muslim countries.

Mental ill health and unemployment

How are we to interpret the difference in the association between mental ill health and unemployment in immigrant women and in immigrant men?

After the Second World War, Sweden went from being a country of emigration to being a country of immigration. The rapid development of Swedish industry in the 1950s and 1960s created a large demand for labour in Sweden which was initially solved with immigrant workers. With the international recession and increased unemployment in the early 1970s, worker immigration diminished, only to be replaced by refugee immigration.

The fact that foreign-born individuals are on average at greater risk of unemployment seems primarily to be a consequence of a general rise in unemployment in Sweden, which hits immigrants harder than Swedes, partly because of discrimination. Throughout the period of worker immigration, about half the immigrant workers were women. The women worked both in female-dominated occupations, such as domestic service and healthcare, and also in industry. During the period of worker immigration, foreign women had a higher rate of employment than Swedish-born women. Today the situation is the opposite, and foreign-born women have a lower rate of employment than either Swedish-born women or foreign-born men.

Cultural background is often used to explain why foreign-born women nowadays have the lowest rate of employment. According to the proponents of this theory, the women's culture stands in the way of their ability to enter the labour market.

However, research on earlier immigration to Sweden helps one to see that women's homeland culture seems to be a poor explanation for their low rate of employment. Several countries have been the country of origin for both immigrant workers and refugees to Sweden, e.g. Poland, Turkey and Yugoslavia/former Yugoslavia. It is clear that, although women from Yugoslavia came and worked in Sweden as early as in the 1960s, women from Bosnia (i.e. former Yugoslavia) often have difficulty finding work in Sweden today.

Not only is the rate of employment lower among foreign-born women, they also have a higher rate of ill health than Swedish-born women and foreign-born men (for an overview see Lindencrona et al., 2006). Westman (2006) found that the risk of attempted suicide, suicide and hospital admissions for mental illness was often higher in Sweden if you were born in another country. Do the high levels of mental ill health explain the high rate of unemployment among foreign-born persons in general and foreign-born women in particular? A study by Klinthall (2008) investigated the risk of serious illness in all immigrants in Sweden compared to the Swedish-born population. It found that, if you control for socioeconomic factors, the much higher risk of serious illness in immigrants disappeared. Tinghög and co-workers (2007) arrived at similar results when investigating the risk of mental ill health in foreign-born and Swedish subjects.

Many studies have explored the association between unemployment and mental ill health. In the 3,500 persons studied by Nordenmark (1999), the causal relationship appeared to be that people's mental health deteriorated when they became unemployed rather than there being a health-related selectivity for work – something also found by Klinthall (2008) in studies of immigrants in the Swedish labour market. A qualitative study from Latvia shows that unemployed and self-employed women experienced breadwinner responsibility as a positive factor for mental health. Although some studies show that work may be linked to mental ill health in women, there is much to suggest that women derive health benefits from working.

Since the association between mental ill health and unemployment is so strong, and much of the mental and somatic ill health disappears if you control for socioeconomic factors, it seems more likely that ill health among foreign-born women is not an explanation of why so few of them work, but a consequence of it. Moreover, many foreign-born women in the labour market have had heavy, strenuous jobs and have therefore suffered wear-and-tear injuries which have in turn led to sick leave.

What is a plausible explanation for the failure of foreign-born women to enter the Swedish labour market? Akhavan (2006) in her dissertation concludes that socioeconomic factors, discrimination and racism are important explanatory factors for unemployment and high rates of sick leave among foreign-born women. To clarify this issue, research is needed not only into the high risk of mental and somatic ill health among foreign-born women and its association with unemployment, but also into women refugees' reasons for seeking asylum and the consequences of these for mental ill health.

Better support

How can the efforts to address mental ill health in refugees and asylum seekers, from overarching issues to specific measures, be improved in practice?

In *Integration and public health – a knowledge overview*, a knowledge compilation for the 2005 Integration Report, Lindencrona and co-workers (2006) draw attention to deficiencies in the diagnosis and documentation of mental conditions in asylum seekers which can lead to both over- and undertreatment. It is unclear how this problem should be addressed in the absence of statistics on the outcome of the health interviews with medical tests offered to every newly arrived asylum seeker. In other words, we do not know how new asylum seekers feel on arrival, either mentally or physically. According to the knowledge compilation, the conclusion of clinical experience and smaller studies is nevertheless often that mental health status is poorer in asylum seekers than in all other immigrant groups. This means that there is a risk that new arrivals may quickly become marginalised. Under the new Health and Medical Care for Asylum Seekers and Others Act of 1 July 2008, adult asylum seekers are only entitled to acute care and treatment that cannot be postponed. Hidden or undocumented refugees are entitled to acute care but must pay for it themselves.

Since adult asylum seekers have a limited right to care, their social network – often their friends – have to tell them what is available for them to take to feel better. In the worst case this can

lead to tablet and/or alcohol abuse. Illiterate persons run an extra high risk of drug dependence because they cannot read directions and take the wrong dose. Against this background it becomes important to study the stress and the options experienced by asylum seekers in connection with their reception as refugees.

Following a study at a psychiatric outpatient clinic in a immigrant-dense neighbourhood, Lindencrona and co-workers (2001) concluded that many newly arrived refugees are in need of coordinated professional services to help them find living quarters, access to the labour market, good language training, a strong anchoring in Swedish society, and healthcare services. According to the authors, this highlights how difficult it is for public organisations to work across customary professional and administrative boundaries.

A study from Malmö shows that many who attend Swedish for Immigrants (SFI) courses have difficulties in concentrating and sleeping – symptoms that make learning harder and thus prevent them from learning Swedish and, later on, from getting work experience and becoming self-supporting.

How then can we create a health-promoting refugee reception process?

First, we need a paradigm shift to move from a problem-based approach to a resource-based approach. It is also of the first importance to investigate and identify methods that are ineffective, not cost-effective, or unethical to implement. The next step is to create an evidence base for the methods used.

Health-promoting and health-preventative work among asylum seekers has been neglected despite the availability of evidence-based methods that could be tested on a broader scale. One proposal for evidence-based health-promoting refugee reception is the 4K public health work strategy applied in a three-year project at Botkyrka and funded partly by the European Refugee Fund (www.stressforskning.su.se). The 4K strategy, which is anchored in the health-promoting work of the World Health Organisation (WHO), can be summarised as Municipal collaboration, Knowledge development, Client

adaptation and Qualified care (in Swedish: Kommunal samverkan, Kunskapsutveckling, Klientanpassning och Kvalificerad vård).

Examples of preventative measures

One example of evidence-based health-promoting and health-preventative measures for asylum seekers are the health interviews with medical tests (taking of samples) that should be offered by the Swedish Migration Board at the introduction unit as part of the refugee processing. These interviews are generally conducted by a registered nurse, or in some counties by a physician at a health centre. Family members who arrive within the two-year rule should also be offered health interviews and medical tests by their municipal case worker. Depending on the outcome, the nurse will refer the person along the care chain as appropriate to the nature of the problem. The National Board of Health and Welfare has stressed the importance of health interviews for asylum seekers in various documents and reports. However, the most recent statistics show that only 65 per cent of all asylum seekers in Sweden went through health interviews with medical tests in 2008; in Stockholm County the figure was 45 per cent (Swedish Association of Local Authorities and Regions, 2008). There are currently no systematic compilations of health interviews with persons who are asylum seekers before they obtain permanent residence and receive their community introduction, the aim of which is for them to become self-supporting.

Another method to reduce the vulnerability of asylum seekers is group-based health information. This method is now undergoing quality assurance with asylum seekers at the Swedish Migration Board with promising results. A further method is health school for newly arrived refugees during their introduction. This is an innovative, evidence-based approach created at Harvard which is also undergoing quality assurance at present by a process of determining the effect of the preventative measures. The aim is to offer refugees ‘psychoeducational measures’ in group form at an early stage in the migration process. Measures of this type involve explaining to the refugees the most common symptoms such as sleep

and concentration problems. They are also given tools for managing stress and information about what healthcare resources are available to them.

The course is conducted by healthcare personnel who normally work with individual patients, but who function as teachers on the course, together with an interpreter.

There are also other strategies for reducing the symptom burden of mental ill health during the asylum and introduction process. The asylum process should for instance be as brief as possible, and all should be entitled to receive the care they need. According to Associate Professor Hans Peter Søndergaard, Medical Director at the Centre for Trauma and Crisis, Danderyd Hospital, one form of relief during the introduction could be to adapt the time of the SFI course, for instance offering afternoon classes to those with sleep problems, or to offer part-time sick leave.

The need to disseminate knowledge

How can we disseminate knowledge about a health-promoting introduction among those who come into contact with asylum seekers and newly arrived refugees?

There are so-called ‘real keenies’ who take up the transcultural perspective in healthcare training programmes, but it is not a compulsory subject. This is a problem, since asylum seekers and refugees, because of their vulnerable position in society, are hit extra hard by lack of competence and cooperation in the care chain. For this reason it is important that students who will be working with asylum seekers and refugees, and those who in other ways come into contact with asylum seekers and refugees, are given the necessary knowledge and further training in the skills required for working in multicultural care.

Competence development could include:

- Information about respect for and understanding of the competences, responsibilities, values and tasks of the different actors involved as well as opportunities for creating a shared platform.

- Transcultural nursing care, transcultural psychiatry and refugee psychiatry including evidence-based interventions and methods of quality assurance (particularly migration-specific stress symptoms such as PTSD, depression, cognitive memory and sleep disturbances, and identification of protective factors) with a clear gender perspective.
- Attitudes towards and reception of the target group and family members who owing to their exposed situation are more or less autonomous, e.g. they depend on society in order to live.
- Information about the work carried out by user organisations and voluntary organisations in refugee reception.

Municipalities and county councils have primary responsibility for health and social care of persons with mental illness and/or mental functional impairment. However, many evaluation, follow-up and supervision reports point to a lack of coordination and cooperation between the parties involved. Providing health and medical care on equal conditions for all requires as a prerequisite that patients from linguistic, ethnic or religious minorities receive special attention. The significance of a view of humanity and a set of values becomes particularly important in the care of foreign-born persons with mental ill health. The risk of stereotyped preconceptions, misdiagnosis and incorrect treatment is particularly high in the care of asylum seekers and refugees.

Research priorities

What are the priorities for research? One area where research is urgently needed is in describing and understanding what effects could be achieved through appropriate cooperation between the various actors involved and newly arrived asylum seekers and refugees and their families. Quantitative and qualitative studies focusing on the needs of newly arrived asylum seekers and refugees are welcome and should preferably be repeated periodically to monitor developments, compare, and provide needs-adapted

documentation for prioritisation of measures to be implemented and quality assured.

Protective factors are another important area of study. They may affect the health of men and women differently. Support from other people appears to be the most critical factor for perceived health. Studies of more or less enforced separations (e.g. children and parents who are not permitted family reunification because the children are over 18) and divorce, and how this affects the perception of support, would therefore be important. The ultimate lack of support from others is domestic violence, so studies of this would also be valuable. A longitudinal study on gender aspects of protective factors should also provide answers to questions about differences in mental ill health among foreign-born men and women.

In the research and discussion of foreign-born women in working life, it often emerges that research results have been influenced by the researcher's and society's prejudices. To ensure that our efforts on behalf of these women asylum seekers and refugees are appropriate, it is therefore of the first importance that we as researchers avoid falling into that trap, and attempt instead to investigate the reception and living conditions of these vulnerable women without preconceptions.

The methodological challenges consist of trying to understand the specific transcultural and migration-related psychosocial factors for mental health. Complex questions to be answered in future studies are:

How can women asylum seekers and refugees be given a voice in the research, in order to reduce the risk of misinterpretation or being led by prejudice?

How can we achieve more equitable access to resources that are essential for the health and wellbeing of all?

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The anxious brain in men and women

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More women than men suffer from anxiety disorders. Differences are marked in several countries and cultures, suggesting biological mediation. In our project we study brain reactions in women and men suffering from anxiety due to phobias and the significance these reactions have for the brain's internal communications. Our studies indicate that brain regions generating anxiety are more active in women. The results may lead to better treatment and eventually make it possible to prevent anxiety.

Almost everyone experiences anxiety at some time in their life. It may be that unpleasant feeling you get when you are about to pay for something in a shop and find that your wallet is missing, or when you receive bad news. It is not entirely easy to give a comprehensive definition of the concept of anxiety, but it is often described as a feeling of uneasiness, fear, worry or dread. The intensity of the feeling can vary from mild unease to full-blown panic. Anxiety, like other emotions, can be broken down into

various components. The first is becoming aware of a situation and quickly assessing its meaning. A second component is the subjective experience of a negative feeling. A third component is experiencing physiological responses such as sweaty palms or racing heart beat. The emotion is also reflected in bodily alterations like facial expressions. Yet another component is preparing for action; if we are in danger, this means fleeing or attacking whatever is threatening us. Eventually, we are able to control or regulate our emotions to varying degrees so that emotional equilibrium is restored. The anxiety is often short-lived and situation-related, but it can also be described as a trait in certain individuals, who are then referred to as ‘anxiety-prone’.

‘Fear’ and ‘anxiety’ are often used interchangeably despite their conceptual differences. One difference is that fear, unlike anxiety, is externally triggered – you are afraid of something. Anxiety is more diffuse. With fear, you also have clearer options for action – i.e. you can do *something* about it – whereas anxiety often arises when you cannot influence a situation. Reacting with fear or anxiety is how humans and animals respond to a threat. The moment we feel unease and discomfort, the body gets ready for action. This fulfils an important survival function in potentially dangerous situations.

From an evolutionary point of view it is easy to understand that fear has been adaptive for humans. We have been formed to act quickly when faced with a threat: such as if, during a walk in the woods, we suddenly encounter a bear. Our pulse races, blood pressure rises, sweating increases, muscles become tense and oxygen uptake increases. Furthermore, stress hormones such as cortisol, adrenaline and noradrenaline are released. The body quickly prepares for fight or flight and it does this through the activity of the brain, which sends signals to the autonomous nervous system. The two subsystems of the latter – the sympathetic and the parasympathetic nervous systems – control the body’s energy levels; they prepare the body for action and dampen the reactions once the danger has passed.

Anxiety is usually a normal reaction to an unpleasant event, but many people experience fear or anxiety in circumstances where it is not appropriate. From an evolutionary perspective, the ability to feel fear and anxiety has increased our probability of surviving as individuals and as a species. For this to work, we cannot always be too precise about our reactions, so they may also be triggered by harmless events, such as when we are startled by an unexpected noise. Some people have an oversensitive reaction system which is activated too frequently and also in situations where it is unjustified. For them, the emotional reaction becomes exaggerated and irrational, leading to suffering and restrictions on their lives. Anxiety becomes an unwelcome tormentor that is out of proportion to what is happening. In such cases we speak of pathological anxiety, or anxiety disorder.

Anxiety disorders

Many people suffer so badly from anxiety that their quality of life is compromised. It is estimated that up to 30 per cent develop an anxiety disorder at some point in their lives, women more often than men. DSM-IV (*Diagnostic and Statistical Manual for Mental Disorders, 4th edition*) is a diagnostic manual used worldwide in the assessment and diagnosis of psychiatric and psychological problems. The manual establishes criteria for what constitutes an anxiety disorder and distinguishes between seven main anxiety diagnoses: specific phobia, agoraphobia, social phobia, panic disorder, post-traumatic stress disorder, generalised anxiety disorder and obsessive-compulsive disorder. Table 1 summarises the manifestations of the disorders and the lifetime risk for men and women to develop them.

There is significant co-morbidity (co-occurrence) between anxiety disorder and depression. Anxiety also increases the risk of premature death and illness from, for example, neurological and cardiovascular disease – and, perhaps above all, from suicide; the latter especially in a person who suffers not just from anxiety but also from depression.

Table 1. Prevalence of anxiety disorders in men and women in the general population.

Syndrom	Prevalence (%)		Main problem
	Män	Kvinnor	
Specific phobia ¹	7	16	Fear of something circumscribed, such as: animals (e.g. spiders, snakes), heights, air travel, confined spaces, blood, injections
Agoraphobia ¹	4	7	Fear of being in crowded places or away from home, e.g. in a crowd of people, in public or unsafe places, buses or subway trains
Social phobia ²	12	18	Fear of scrutiny or being in the focus of attention, e.g. when giving a speech or presentation, at meetings, parties and social gatherings
Panic disorder ¹	2	5	Recurrent panic attacks, i.e. an overwhelming and sudden anxiety reaction, often combined with agoraphobia
Post-traumatic stress disorder ²	4	7	Disturbing memories and anxiety reactions after an extremely stressful event, e.g. events of war, robberies, violence, accidents
Generalised anxiety disorder ¹	4	7	Pronounced tension and unease in the face of everyday events, e.g. constant anxiety about one's health or finances
Obsessive–compulsive disorder ¹	2	2	Recurrent, unpleasant compulsive thoughts and/or actions such as washing hands over and over or checking things repeatedly

1) USA; 2) Sweden

What are the causes of anxiety disorders? Many researchers believe that reactions in anxiety disorders are learned, e.g. through watching as a child how parents, siblings or others express fear in certain situations. Learning can also result from being warned by others or processing information that one finds unpleasant. However, there is also a genetic predisposition for anxiety disorders. Studies have estimated that the genetic component accounts for about one-third of the variability in anxiety between individuals. Some theories suggest that anxiety disorders develop through associative learning – known as conditioning – and that it is easier to learn to fear some situations than others.

Most specific phobias could potentially have a survival value: for example, an individual who stayed away from venomous snakes and spiders had an increased chance of passing on her or his genes, whereas those who did not watch out did not pass theirs on. Similarly, fear of open spaces could conceivably help you avoid situations where you would easily become prey, just as fear of being confined in small spaces makes it easier to flee in the event of an attack. It could also be imperative to be able to recognise threatening individuals quickly, so as to get oneself to a position of safety and avoid being expelled from the group.

There is some evidence that many of these situations are more readily associated with fear than others. One way to study such fear learning experimentally is to pair an electric shock or some other unpleasant experience to an image. It is then easier to develop so-called conditioning to snakes and spiders than to flowers or mushrooms, for instance. It is also easier to develop fear conditioning to an angry face than a happy one. Evolution may well have shaped our genome in a way that biologically prepares us to acquire fear easily to certain stimuli. This theory could explain why phobias develop to snakes, for instance, but not to cars. There is no genetic basis for developing car phobia, because cars are hazards that arrived late in our evolutionary development.

If two persons experience fear in the same situation, one may develop a phobia and the other one not, so experience is not

everything. Perhaps there are individual variations in conditionability that are related to heredity and environment (the nature/nurture debate). For example, there may be an interaction between heredity and environment such that those who develop fear conditioning more easily are at greater risk of developing problems than those who have difficulty learning anxiety and fear. Fear conditioning, in both animals and humans, has a genetic component, and about half the differences in conditionability can be ascribed to heredity.

Sex differences in anxiety disorders. Women are on average twice as likely as men to develop an anxiety disorder. We still do not know why. Studies of sex differences in conditioning mechanisms provide little support for heredity being more important in women or men. Both genetic heritage and environment influence the brain, and sex differences may become easier to understand if we study intermediary or underlying mechanisms rather than focusing directly on behaviour. Brain activity could provide a link between genetic characteristics and environmental factors in anxiety and anxiety disorders. It could even be the case that anxiety symptoms are driven by different brain mechanisms in men and women, and that the most important differences are found in the brain and not in behaviour.

Brain and anxiety

There is an urgent immense need to determine how anxiety arises, how it can be treated and prevented, as well as to understand why women are affected more often than men. To do this successfully, we need to seek detailed knowledge about how unpleasant emotional experiences arise in the brain and whether the mechanisms are different in men and women.

As early as 1937, James Papez described a neuroanatomical network for emotional life. During the 1950s, Paul McLean suggested that the limbic system is the area of the brain responsible for regulating emotions. The limbic system forms a ring around the thalamus centrally in the brain and consists of a number of

structures such as the amygdala, hippocampus, hypothalamus, cingulum and septum.

In the past 20 years or so our knowledge about the brain and emotional life has increased considerably, and we now speak of *affective neuroscience* as a separate scientific discipline. To understand the processes, we need to know how the brain works in different situations, what function the different parts of the brain have, and how they work together.

Amygdala. In terms of fear and anxiety, much of the research interest has focused on the temporal lobe and the nuclear group of the amygdala. In the 1930s Klüver and Bucy described so-called emotional blindness in rhesus monkeys which after a temporal lobe lesion appeared to lose their ability to recognise and react to things that normally arouse fear in these animals. A large number of studies have subsequently provided strong evidence that the amygdala is activated when we learn about and react to something dangerous. The amygdala can be described as an ‘emotional modulator’ that gives incoming stimuli their emotional meaning.

On sensory stimulation, nerve impulses normally travel from our sensory organs to the thalamus and then on to the brain cortex for evaluation and processing. The American emotion researcher Joseph LeDoux used anatomical tracking techniques to show the existence of a projection pathway leading directly from the thalamus to the amygdala. LeDoux believes that the visual impression, for instance of a snake, or of a face showing emotions, can reach the amygdala via the direct route before the information has been processed in the visual cortex. This allows the amygdala to trigger a ‘fight-or-flight reaction’ before the brain cortex has had time to create conscious awareness. Fear then arises instantaneously and precedes conscious thoughts and voluntary actions. When confronted by something that evokes fear, persons with phobias therefore experience strong fear which cannot be prevented with the help of reason. The person becomes so to speak emotionally ‘hijacked’ by the amygdala.

Through pathways to other brain structures, the amygdala then directs muscular and visceral activity and contributes to the arising of a conscious emotional experience.

Hippocampus. The amygdala has been called the hub in the wheel of fear, but other areas of the temporal lobe also have important functions in fear and anxiety. For example, there is a reciprocal exchange of information between the hippocampus and amygdala when the emotional meaning of certain stimuli is being learned. It is probably the *hippocampus* that ensures that we remember the context of situations where emotions arise, while the amygdala creates the actual emotional memory. The British professor of psychiatry Jeffrey Gray has pointed out that the behavioural effects induced by hippocampal injuries in laboratory animals are similar to those resulting from the administration of anxiolytic (anxiety-reducing) drugs. According to Gray, the hippocampus plays a central role in the so-called *behavioural inhibition system*, which in threatening situations causes humans and animals to stop, cease ongoing behaviours, and focus their attention while experiencing physical reactions such as palpitations during the assessment of the situation. If the threat is real, this state can rapidly transform into action, such as fleeing from the situation, or fighting and mounting a counterattack if no other options exist. Anxiety reactions then, can be understood as hyperactivity of the behavioural inhibition system, and anxiolytic drugs damp down the activity in this system.

Cortical areas. To a large extent it is activity in the frontal lobe, i.e. prefrontal cortical regions, that underlies both the conscious experience of being frightened or anxious and the thoughts and perceptions that are linked to this negative feeling. The prefrontal cortex includes a large part of the brain and has various sub-areas which contribute to our ability to perceive, evaluate and react to emotional stimuli. Our understanding of these processes is still superficial, but we do know for instance that the lower surface of the frontal lobe (orbitofrontal cortex) has projection pathways to

the amygdala and is an area important for emotional regulation. The orbitofrontal brain cortex may for instance be responsible for reducing the activity in the amygdala, and hence reducing anxiety. Injuries to this part of the brain can lead to personality changes and impairment of impulse control, decision-making ability, social skills and regulation of affect.

Yet another area of interest to emotion researchers is the insular cortex. The insula is known to have projection pathways to several areas that are of importance for emotions, including the amygdala and hypothalamus. The insular region is moreover one of the main receivers of nerve impulses from our autonomous nervous system and viscera. The insula alerts us when it detects disequilibrium in body functions, and has a regulating effect on physical expressions of emotions, such as heart palpitations and sweating.

Alarm and control systems. To summarise, structures in the temporal lobe, including the amygdala and hippocampus, probably act as an *external alarm system* – a watchdog against the surrounding world that barks when it senses danger in the outer environment, thereby mobilising our body for fight or flight. The insular cortex and hypothalamus are in turn part of our *internal alarm system* – the watchdog that barks if our body's internal environment changes excessively, for instance when the heart races and blood pressure rises abnormally. In addition we have *control systems* in the prefrontal cortex, including the anterior cingulate cortex, which can be likened to the dog owner's tightening the leash and restraining the watchdogs when they bark, so as to be able to regulate the emotional reaction. Anxiety disorder can be caused by malfunctions in our alarm or control systems.

Sex differences and brain anatomy. It has been speculated that anatomical differences between the male and female brains could underlie the increased incidence of anxiety in women. The associations between sex, brain structure and anxiety disorders are nevertheless complex. There are differences in brain volume

between the sexes which may be significant. Women on average have a smaller brain volume than men, but a larger proportion of grey matter. Men consequently have a larger proportion of white matter. Women also have a faster metabolism and higher brain perfusion than men. In addition, there are differences in certain specific structures, such as men having larger amygdala nuclei. A Japanese study recently showed that the size of the amygdala and insular cortex differed in women and men suffering from panic anxiety. The hypothalamus, another structure of importance for stress and the regulation of stress, is also larger in men. Women, on the other hand, have a larger caudate nucleus, a structure important for a great many functions including motor functions, mood and learning. The hippocampus, which is important for memory consolidation, is generally larger in women than in men.

There are thus many variations in the structure of the brain that may be of significance for anxiety and more generally experiences of unease and that seem to differ between men and women. It is also conceivable that the sensitivity or reactivity of network structures important for anxiety disorders may differ in men and women, and that functions irrespective of size are important for understanding sex differences. In studies where researchers showed men and women images that evoke emotions and at the same time recorded their brain function, a pattern emerged showing that men more often react more with one hemisphere of the brain than women, and women react more strongly in the brain stem. Recently, an Italian study showed that women activate emotion-generating areas to a greater extent than men when they look at images of people who are suffering. This may perhaps reflect greater empathy.

Methods for studying brain activity in anxiety

Brain imaging studies allow us to study brain activity at rest and during different types of stimulation. These kinds of measurements can give information about the brain's structure and function, and about its electrical, magnetic and metabolic processes. The studies can also teach us how information is transmitted in the brain, i.e.

they can teach us about neuroreceptors, neurotransmitters and nerve activity. While most imaging methods give cross-sectional images of brain function and structure, they differ in many other respects including image resolution and how long it takes to make the measurements. Each method has its advantages and disadvantages.

One method is called *positron emission tomography* (PET). PET studies use radioactive trace elements such as oxygen-15-labelled water to measure regional cerebral blood flow (rCBF) in the brain. The higher the blood perfusion, the higher the information transfer (synaptic activity). Another tracer, fluorine-18-labelled fluorodeoxyglucose (FDG), can be used to determine glucose (sugar) metabolism in various parts of the brain. Glucose is the brain's fuel.

SPECT (single photon emission computed tomography) is technically simpler than PET but works on similar principles by using radioactive tracers to measure for instance cerebral blood flow and glucose metabolism.

Another technique, functional magnetic resonance tomography (fMRI), is based on the fact that strong magnetic fields can be used to measure oxygen content in blood. Differences between oxygen-rich and oxygen-poor blood generate the so-called BOLD signal, which co-varies with nerve activity. By studying BOLD signal changes, e.g. in anxiety reactions, one can locate the structures and networks associated with the feeling of anxiety.

To investigate emotional processes, *activation studies* are most often used, where an activated state, e.g. nerve activity in an anxiety-producing situation, is compared with rest or with some other control condition. For example, in the case of specific phobias one can register brain activity – usually by fMRI or PET – while showing images of snakes or spiders. Results are then compared with the corresponding activity when neutral images are shown. In social phobia, anxiety can be studied during or just before an occasion when the person has to perform or speak in public. In panic disorder, panic attacks have been triggered experimentally by administration of procaine, yohimbine or lactic acid. In post-traumatic stress disorder (PTSD), anxiety is often studied during exposure to sounds

or images of war or other stimuli that function as trauma reminders. One can also compare how persons with anxiety disorders and healthy individuals process emotional information, e.g. facial expressions showing emotion, or how emotional memories are formed and expressed.

PET, SPECT and fMRI can all be used to study the brain's activity profile at rest and under stress. These different techniques allow us to measure and quantify both cortical and subcortical changes, i.e. changes in the brain's outermost sheet of neural tissue (the cortex) or in the structures that underlie it. There are also techniques that are mostly limited to cortical imaging, among them xenon-133 inhalation, quantitative EEG (electroencephalography) and MEG (magnetic encephalography). Furthermore, there are also techniques that visualise the structural properties of the brain, such as computed tomography (CT) and structural MRI. The distribution of nerve fibres can be studied by a process known as tractography using diffusion tensor imaging (DTI).

Brain imaging studies of anxiety disorders

Many imaging studies have shown the brain areas mentioned above – amygdala, hippocampus, orbitofrontal cortex, anterior cingulate and insula – to be functionally connected and important for the activation and regulation of emotions. One would therefore expect the anxiety disorders to be associated with altered activity in these areas of the brain. However, the activation patterns are not entirely identical in the various anxiety diagnoses, since the symptoms of the individuals affected differ, as, probably, do the underlying abnormalities in the brain.

Phobias. PET and fMRI studies of social phobia suggest that sensitivity in the amygdala region is increased in patient groups compared with non-anxious control groups when processing frightened or threatening facial expressions. The same is true in classical conditioning when unpleasant associative memories are formed. We have studied how brain activity changes when persons

with social phobia speak in front of a group and experience severe anxiety while doing so. In the phobia group, the anxiety reaction corresponded to increased activity in the right amygdala complex compared to a control group. Apprehension anxiety, measured before the anxiety-inducing speech, also corresponded to increased activity in the amygdala. This suggests that persons with social phobia may have a hypersensitive external alarm system.

In some imaging studies it has been observed that social phobia is associated with reduced frontal lobe activity. This could mean that it is harder for the brain to down-regulate the unease caused by social situations. Several PET studies of animal phobias have also shown reduced frontal lobe activity during intense fear. People with a phobia for snakes or spiders show massive reductions of blood perfusion in the frontal lobe when, for example, viewing film sequences of snakes or spiders. The reduced frontal lobe activity probably leads to a loosening of the emotional control over the amygdala and the brain's alarm systems, resulting in severe anxiety.

It is well established that the frontal lobe is important for higher cognitive functions, and in neuropsychology there are several tests to measure frontal lobe function. One is the Stroop test, which is based on colour words where the colour conflicts with the word, e.g. the word 'green' is printed in red. Persons with specific phobias perform considerably worse than control subjects in the Stroop test when the colour words are presented against a background video showing either snakes or spiders, presumably because their frontal lobe functions are compromised during the exposure. There are also findings indicating that the amygdala is activated more when persons with a spider phobia look at spiders compared to when they look at neutral stimuli such as mushrooms, and that the activation level is higher than in non-anxious control subjects.

Post-traumatic stress disorder. Several brain imaging studies in patients with post-traumatic stress disorder (PTSD) have found that anxiety symptoms are triggered when stimuli are presented that are reminiscent of an earlier life-threatening trauma, which corresponds

to heightened amygdala activity and reduced activity in parts of the frontal lobe (prefrontal cortex). There is also a co-variation such that increased activity in the amygdala and reduced activity in the medial prefrontal cortex often correspond to more severe illness. American researchers at Harvard University have shown that the amygdala reacts more easily in patients with PTSD when they look at frightened faces than in control subjects who have also experienced a trauma but have not developed the anxiety disorder. The amygdala reacts even when the patients are not conscious of the frightened facial images. This can be studied by showing the image of the frightened face very briefly, followed directly by another, masking image (e.g. a neutral face) for a longer time. The person will then only experience the masking image, but the amygdala still reacts to the unconscious target image. It has not been determined whether the brain activity patterns in PTSD are an effect of the trauma or predate the trauma and may make the individual sensitive to developing the anxiety disorder.

Changes in the structure of the brain have also been observed in post-traumatic stress. From animal studies it is known that severe stress causes the hippocampus to get smaller, and in several MRI studies a smaller hippocampus volume has been described in persons with PTSD. Some studies have also shown that hippocampus volume is linked to unpleasant war experiences, where prolonged exposure to war situations is associated with a smaller hippocampus. The causal chain has been called into question by Roger Pitman and co-workers at Harvard University, who in a twin study found hippocampal size to be a risk factor for developing PTSD rather than an effect of the anxiety itself. Longitudinal studies, where hippocampal volume is measured over time and used to predict the development of PTSD, could provide a better understanding of the causal relationships.

Panic disorder. Panic disorder was the first anxiety disorder to be studied using brain imaging methods in the mid-1980s. Eric Reiman and colleagues found among other things that panic triggered by

lactate corresponded to increased blood perfusion in the anterior temporal cortex, insula and basal ganglia. Several research groups have used PET to study the effects of other substances that trigger panic. No uniform results and no definite pattern differentiating women from men have emerged.

Obsessive-compulsive disorder. PET studies investigating glucose (sugar) metabolism at rest have shown that patients with obsessive-compulsive disorder (OCD) have a raised metabolism in the part of the brain known as the caudate nucleus. Activation studies in which attempts were made to provoke symptoms, e.g. by exposing persons with a washing compulsion to dirty objects, have found increased or altered activity in the orbitofrontal cortex, anterior cingulate, striatum (which includes the caudate nucleus) and thalamus, among others. In contrast to social phobia and PTSD, for instance, it has not been convincingly demonstrated that people with OCD have heightened sensitivity in the amygdala area or the medial temporal lobe. This may not be so surprising since the symptomatology of OCD is complex and markedly different from other types of anxiety disorder. The brain network that most seems to be abnormal in OCD includes the striatum, thalamus and cortical areas of the frontal lobe.

Generalised anxiety disorder. While there have not been many studies of brain function in generalised anxiety, it has been reported that glucose metabolism at rest is elevated in the occipital lobe, temporal pole and some frontal areas, especially in the right brain hemisphere. In an fMRI study where children with generalised anxiety viewed emotional facial images, amygdala reactivity was higher in the anxious children than in a control group. It was also found that amygdala activity co-varied with the severity of the anxiety. An earlier study of structural abnormalities also reported a larger amygdala volume in children with generalised anxiety.

Sex differences and anxiety-related brain activity. It is not known whether the emotional activity in the brains of people with anxiety

disorder differs between men and women. Many studies, e.g. of specific phobias, have focused almost exclusively on women. One simple hypothesis is that the nodes in the brain's fear network are more active in women than in men. In preliminary findings from a study, we have recently observed higher neural activity in the amygdala of non-anxious women than men when viewing emotional as compared to neutral faces.

Treatment of anxiety disorder

Drug treatment. Quite a few pharmacological preparations are helpful for anxiety. *SSRIs* (selective serotonin reuptake inhibitors) *balance* the levels of serotonin in the brain and are today the most common group of drugs for depression and anxiety. There are related drugs that also affect noradrenaline (e.g. *venlafaxine*). SSRIs had their breakthrough in the early 1990s and offer many advantages, including that their side effects are usually well tolerated. Before that, *benzodiazepines* were the most common type of drug for treatment of anxiety. These preparations are still used as needed since they have a rapid effect. However, benzodiazepines are no longer recommended as first-line treatment in anxiety since they can be addictive and carry the risk of abuse.

Other drug categories that can be helpful in anxiety include beta blockers, which are really medications for high blood pressure and heart failure. Beta blockers can reduce bodily reactions of nervousness, for instance when a person with social phobia is giving a presentation. *Monoamine oxidase inhibitors* inhibit an enzyme which breaks down serotonin, but are nowadays used considerably less often than SSRIs. There is some interesting research going on around newer types of anxiolytic drugs, for instance those which chemically block releasing hormones such as CRF (corticotropin releasing factor) or neuropeptides such as substance P.

Psychotherapy. The form of psychotherapy with the best documented effect in anxiety disorders is cognitive behavioural therapy (CBT). This is a structured and goal-oriented treatment that tries to

change a person's existing problematic behaviours and thoughts. CBT has achieved excellent therapeutic results in conditions such as specific phobias (e.g. fear of snakes, spiders or heights). After initial assessment, the actual treatment can be carried out in a single session of about three hours' duration. For other anxiety conditions the treatment takes longer, but 10–15 weeks of therapy is usually enough for the person to experience significant improvements. An important element of cognitive behavioural treatment of anxiety is exposure, i.e. that the person is gradually exposed to what they fear. Most often exposure is combined with cognitive therapy aimed at changing negative thoughts and ideas that occur before, during and after an anxiety-triggering situation. Often the person has got stuck in a vicious circle of negative thoughts, physical nervousness and anxious avoidance behaviour, which the therapy tries to break.

How does treatment for anxiety affect the brain?

We still have very limited understanding of the mechanisms of effect of anxiety treatment on the brain. One might perhaps anticipate that effective treatment 'normalises' the alarm systems and reinforces the control systems. Neural activity would then diminish in areas such as the amygdala and insula and alter activity in the anterior cingulate, the orbitofrontal and medial prefrontal cortices.

It is also conceivable that treatment does not normalise activity at all, but compensates for 'pathological' networks by influencing entirely other areas. It should be borne in mind that the effects of treatment can vary depending on who the patient is. This is not just a matter of sex: factors such as the type of disorder, how severe it is and for how long it has existed, and the patient's genetic makeup can also influence the outcome. Effects can also vary on the basis of *treatment factors* such as what type of drug is given, at what dosage and for how long, or the therapist's skill and the treatment components that feed into the psychotherapy. On the other hand, one might well imagine that if the treatment has a strong enough effect on the symptoms (i.e. it relieves the anxiety enough), this effect ought to be measurable in the brain and might perhaps look

the same irrespective of whether it was achieved by drugs or by psychotherapy.

Brain imaging studies of anxiety treatment. PET studies of social phobia have shown that both SSRIs and CBT attenuate activity in the medial temporal lobe including the amygdala and hippocampus, which are hyperactive before the treatment. Patients who responded well to the treatment experienced the greatest reduction in activity in the amygdala and other limbic structures, and these patients were also the most improved at follow-up one year later. Both SSRIs and CBT can therefore achieve alleviation of symptoms by dampening anxiety-generating areas.

Harder to reconcile with the theory that treatment helps frontal control areas to dampen the amygdala is a concurrent finding that activity in the anterior cingulate and prefrontal cortices was reduced. However, this could be a reflection of the fact that the situation is assessed differently after treatment. Other parts of the cortex, where differences were seen between patients and healthy control subjects before the treatment, were unaffected by any of the treatments given. This suggests that brain activity is only partly normalised by treatment. Dampening of amygdala activity after treatment for social phobia has also been shown in tests of substance P antagonists. Amygdala reductions occur even in patients who responded well to the treatment but in the end turned out to have been treated with placebo (pharmacologically inactive treatment).

The fact that psychotherapy and drugs can produce similar effects on brain activity has also been noted in patients with obsessive–compulsive disorder. In the early 1990s, Lewis Baxter and colleagues found that the initially elevated resting metabolism in the caudate nucleus of the right hemisphere was dampened in a similar manner after treatment with either the SSRI fluoxetine or CBT. A subsequent study confirmed that patients who responded to psychotherapy showed greater reduction of glucose metabolism in the right caudate area. Other studies also suggest that both

psychotherapy and drugs influence a striatal–thalamic–cortical network linked to the symptoms of obsessive–compulsive disorder.

Normalisation of amygdala activity after successful CBT has also been reported in a study of spider phobia, although there are other studies of specific phobias where this could not be shown.

There have been a few brain imaging studies of treatment effects in other anxiety disorders, but more studies will be necessary before any clear conclusions can be drawn.

Do men and women respond equally well to treatment? There are some studies that show that women respond better to SSRIs than men. One of the questions this raises is whether the brain's serotonin system differs between men and women who suffer from anxiety. Could such differences then also explain the increased incidence of anxiety in women? This is an important question for future research. As mentioned, there is growing interest in the neuropeptide substance P in the pharmacological treatment of anxiety. Men and women may have different amounts of substance P receptors in certain brain regions and it would be interesting to study the possibility of sex differences in the response to treatment with drugs that have an effect on substance P.

Transmitter substances and anxiety

Several lines of evidence suggest that serotonin plays an important part in normal fear and anxiety as well as psychiatric anxiety disorders. Both animal and human studies have shown that changes in the serotonin system influence emotional behaviour. In addition, both anxiety disorders and depression are treatable with serotonergic drugs.

As mentioned, SSRI treatment has been found to dampen activity in brain areas that are relevant for anxiety, such as the amygdala. Using fMRI it has been possible to demonstrate that this effect can be triggered not only in anxiety patients, but also when SSRIs are given to healthy volunteers. Moreover, the effect is

already evident after just one week of treatment. It is likely that the subjective dampening of anxiety – which occurs only after several weeks of treatment – is preceded by physiological changes in the brain which cause the activity in limbic structures to be directly or indirectly inhibited by serotonin. It is a tempting notion that not only SSRIs but also successful psychotherapeutic modalities such as CBT have a direct effect on serotonergic neurotransmission, although this has not been shown.

Serotonin is not the only transmitter substance of interest in anxiety; in reality, there are many transmitter systems which interact.

It is possible that anxiolytic drugs acting via different transmitter systems nevertheless have a common end station in the brain, in that all of them lead to dampening of activity in areas such as the amygdala and adjacent structures in the medial temporal lobe. CBT also appears to achieve this effect. The symptomatic relief obtained from both pharmacological and psychological anxiety treatment probably corresponds to a reduction of sensitivity in the neuronal network that constitutes the brain's alarm system.

Different transmitter processes in men and women? The neuro-chemical systems described are important for our emotional state. Drugs that influence their function therefore often influence anxiety and anxiety disorders as well. Men and women may potentially differ in some or all of the processes which then take place. Studies on healthy women and men suggest that women have more serotonin receptors than men.

This applies to a specific type of serotonin receptor, serotonin-1A, but there are about ten others that have not been studied. Both slower and faster serotonin reuptake by the presynaptic neuron has been found in women. Contradictory results have also been reported for the dopamine system, with both more and fewer dopamine receptors being reported in women. The same applies to dopamine release. Higher reuptake in women has been described in a couple of concurring studies. It would be most interesting to relate

the neurochemical functions to reactions in the brain's emotional network, in order to see whether there are differences between the sexes in these mechanisms.

Genetic influence on anxiety and brain activity

The question as to why some people are more fearful and anxious than others remains unanswered by science, but the answer must take into account both environmental influences and genetic factors. Studies have shown that anxiety tends to aggregate in families, i.e. the likelihood of being anxiety-prone increases if your mother, father, sister or brother also has such traits. Research in developmental psychology has shown that children's anxiety about exploring new environments – the so-called inhibited temperament style – can be observed very early in some individuals, and that this temperament style is associated with increased neural sensitivity in the amygdala and a risk of developing anxiety disorder later in life. Moreover, an increased incidence of anxiety problems has been observed in parents of children with an inhibited temperament style. Studies of this type, as well as animal studies, support the suspicion that genetic factors influence anxiety disorders. Twin studies comparing monozygotic and dizygotic twins have also demonstrated the existence of a genetic component in fear, anxiety and phobias. For example, it appears that in 30–40 per cent the variability between individuals in social phobia can be accounted for by hereditary factors. This implies that the environment is of major importance and there is likely to be an interplay between genetics and environment in the causal chain, such that for instance a person with inherited sensitivity may have stronger reactions to unpleasant life events and through this be at higher risk of developing an anxiety disorder.

Serotonin-related genes. The gene that codes for the serotonin transporter – the protein which controls serotonin reuptake in the presynaptic neuron – has lately aroused a great deal of research interest. The gene has a so-called functional polymorphism, where

a short and a long allele (repetition sequence) are associated with different degrees of anxiety. Persons who carry the short allele have a lower reuptake of serotonin, resulting in higher concentrations of synaptic serotonin than in people who have the allele with the longer repetition sequence. Several studies have found that individuals with the short allele are more prone to anxiety and have increased amygdala reactivity. When individuals with the short allele look at images of emotional faces, amygdala activation is greater than in those with the long allele. Moreover, when persons with social phobia were studied during a stressful public presentation, amygdala activation was stronger in individuals with the short allele than in those with long alleles. There are also data to suggest that persons with social phobia who carry the short allele respond less well to treatment with SSRIs than persons who only have the long alleles.

Persons who carry the short allele of the serotonin transporter gene also appear to be more easily conditioned, i.e. they have an increased ability to develop fear through associative learning. This indicates that the effect of the gene on anxiety arises in interplay with environmental factors. Depression researchers have similarly found that individuals with the short allele are at higher risk of depression, but only if the person is in addition exposed to severe stress from the environment. By contrast, persons with two long alleles of the gene did not develop depression even if they were exposed to stressful life events.

Genetic research cross-fertilised with brain imaging (imaging genetics) is a field that is developing rapidly, and new genes are constantly being added that are interesting to relate to anxiety disorders and brain functions. For example, studies have found that variations in the tryptophan hydroxylase-2 gene (TPH2), which codes for serotonin synthesis in the brain, also influence how strongly the amygdala reacts to emotional stimulation. When persons with social phobia were treated with either drug or placebo in a double-blind study, variation in this gene was able to predict both the degree of neural dampening in the amygdala after treatment and the degree of clinical improvement achieved with the placebo

pill. It is possible that variation in genes that control processes for serotonin and other transmitter systems may also be related to how well individuals with anxiety disorders respond to psychotherapies such as CBT.

Sex differences and gene-environment effects. Differences between the sexes in their susceptibility to anxiety can arise from genetic factors, environmental influences and the interplay between these. Sex hormones are obviously of special interest for the development of anxiety disorders, since men and women differ in terms of their sex hormones. How oestrogen influences the brain is not well known. A recent Dutch study showed that administration of progesterone, which forms naturally during pregnancy and before menstruation, increases amygdala reactivity in women. Could the hormone profile affect the way women react to negative events, by affecting the brain's stress system? Studies that have reported sex differences in brain chemistry have mostly focused on the monoaminergic serotonin and dopamine systems. Although we cannot state with any great certainty that sex differences in brain neurochemistry determine sex differences in anxiety, there are interesting investigations that have studied how genes that control neurochemical processes can affect behaviours and experiences that are important for anxiety and depression.

With regard to the serotonin transporter gene, we noted earlier that persons with the short gene variant more often react with depression when exposed to unpleasant life-changing events. Similar observations have also been made in connection with substance abuse. What makes this particularly interesting is that it is only women, not men, who appear to be sensitive to environmental influences. Although male genetics do influence brain function to some extent, the interplay with the environment is insignificant, and above all it is in women that the influence of the environment is governed by the genes. Important questions are obviously what may underlie this and whether it can be influenced so as to prevent the occurrence of serious problems.

In conclusion

Fundamentally, anxiety is a normal reaction, but in almost one-third of the population it develops into a disorder which markedly reduces quality of life. Of those affected, about twice as many are women as men. Sex differences can arise as a result of genetic factors and the influence of the environment. By studying the brain we can increase our understanding of how the effects of heredity and environment combine to produce symptoms of anxiety. Important research questions that remain to be answered include how emotional activity in the brain's alarm and control systems differs between the sexes, how anxiety treatment affects the brain, and whether treatment has the same effect on brain activity in women and men. In the future we will be able to combine data from different imaging techniques, such as fMRI and PET, as well as structural and functional measurements of the brain, in order to increase our knowledge still further.

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Stress, health – and illness? – the WISH project

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In the WISH project, four research groups are collaborating to find answers to several questions about stress, health and illness. Ongoing population studies of middle-aged and elderly women are being used to study the effects of today's living environment on women's health. Of interest are above all areas such as the experience of stress and its relation to health and quality of life, as well as associations with conditions such as heart attack, heart failure and stroke. The project is also studying whether quality of life, experience of stress and risk factors for cardiovascular disease in women can be influenced by interventions, i.e. how the healthcare system can actually support women towards a new lifestyle.

We know that there are large differences in the way men and women experience stress, and the WISH project – which stands for Women Investigating Stress and Health – aims to investigate whether there are also differences between men and women in how the experience of stress affects their health.

This is not an easy area to study. The association between mental and physical health is complex. Over the past twenty years,

women have not fully kept pace with men in terms of improvements to health. The difference in mean life span between men and women, which used to be quite large – women lived on average six years longer than men – has in recent decades shrunk by more than two years (Public Health Report, 2009). The differences between the sexes in terms of cardiovascular mortality have similarly become smaller. Over the same period, a growing percentage of the female population has reported symptoms of anxiety and stress (Public Health Report, 2009). We know that some forms of stress can lead for instance to hypertension and elevated blood lipids. These conditions are in turn risk factors for stroke and other cardiovascular morbidity. Can we, by studying different associations in this area, determine whether the increasing experience of stress is one of the reasons why survival has risen more slowly among women than among men during the last ten years in Sweden?

Stress and the experience of stress

Stress and the experience of stress are hard to measure. For a variety of reasons, personality probably being one, different individuals perceive the same level of stress in different ways. There is no good biological method for measuring the experience of stress either. Attempts to measure the degree of stress – for instance by measuring stress hormone (cortisol) in blood and saliva – have not been found to provide a sufficiently reliable measure of an individual's experience of stress. At present, the best way to measure stress perception is simply to ask the person to what degree he or she is experiencing stress.

This has been done in a standardised manner in several population studies. One example is the Prospective Population Study of Women in Gothenburg (known as the PPSW study), which has been going on since 1968. Over 37 years and a total of six follow-up examinations of initially 1,462 participating women, the experience of stress has been registered by asking all participants the same question in the same manner at almost every follow-up (Björkelund et al. 2008). In the WISH project we have used these responses

to compare how different age groups of women have experienced stress, both by charting how each individual has rated the experience of stress in the course of life (e.g. from Cecilia Björkelund age 38 to age 75) and by determining how different generations of women have experienced stress at a given age, such as the percentage of 38-year old women who experienced stress in 1968 compared to 38-year old women in 2004.

The question which was asked explores whether during a given period – at least a month or more – the person had experienced stress in the form of being irritable, tense, nervous, worried, afraid, anxious or sleepless in connection with worries about work, family, health, conflict with the surroundings or for other reasons. Thus we are speaking not of time stress, but emotional stress. What we see is that women report experiencing emotional stress in middle age more often than later in life. What is most striking, however, is that middle-aged women, i.e. women aged 38 and 50, report a rising level of stress since 1980. The stress becomes very pronounced in the 2004 examination. Here almost 75 per cent of women aged 38 and 50 report having experienced emotional stress in the last five years, compared to about 30 per cent in 1968 (Lissner et al. 2008).

Although participation in the latest examination in 2004 was lower than in 1968, it still reflects a significant difference. The major change in society, with women in the workforce rising from 60 to 90 per cent in these age groups, may be one reason why the experience of emotional stress has increased to such an extent (Lundh et al. 2004).

Among the older generations of women in the PPSW study, a clear association was seen between psychological well-being and how well their family was doing. Among younger generations of women, this clear association was no longer evident; here the association was rather between mood and conditions at work (Lundh et al. 2004).

The 2004 examination made a special study of work-related stress and its association with self-assessed health and sick leave patterns in women aged 38 and 50 (Holmgren et al. 2009). About 25 per cent of the women reported a high level of stress at work

and little opportunity to influence their work. Almost 35 per cent stated that work encroached on their leisure time. A higher degree of experienced work-related stress was associated with a higher degree of symptoms of illness, especially stress related to ‘lack of clear organisation’ and stress related to ‘high expectations of yourself and strong commitment’. Sick leave was associated with a high degree of experienced stress which was ascribed to lack of clear organisation and conflicts at work as well as little opportunity to influence their work.

In the 2004 PPSW examination, a special study was also made of women’s self-assessed health and its associations with daily activities, defined as the weighted combination of employment, household and leisure activities (Håkansson et al. 2008). In this generation of women aged 38 and 50, just over half were university educated and 90 per cent had jobs. About half the women assessed their health as good, while somewhat fewer assessed it as not entirely satisfactory. Women who reported a higher degree of balance and manageability in their daily activities were also more satisfied with their lives and experienced less stress. These associations applied regardless of socioeconomic status or age.

Physical health and emotional stress

Comparisons between different generations of women aged 38 and 50 have also raised the question whether increased experience of stress among middle-aged women is behind the increased incidence of abdominal obesity (Lissner et al. 2008). Later generations of women aged 38 and 50 have a clearly better lifestyle in terms of diet, leisure exercise and smoking compared to women of the 1960s, and this is also reflected in the tangible improvement among later generations of women precisely in risk factors that can be influenced by lifestyle. In the PPSW study, the mean blood level of cholesterol and triglycerides was about 25 per cent lower in women aged 38 and 50 in the 2004 examination compared to corresponding cohorts in 1968. Mean blood pressure was lower, leisure exercise had increased and the incidence of smoking had declined from about 40 per cent

to less than 20 per cent (Björkelund et al. 2008). Diet is also much better today, with women today eating less fat and sugar and more complex carbohydrates, protein and fibre than earlier generations (Lissner et al. 2008).

Although BMI, i.e. weight in relation to height, has not increased (despite a mean rise in bodyweight among other age groups such as children and the elderly), abdominal girth has increased in middle-aged women. Our hypothesis is that the concurrent increase in the proportion of respondents who report experiencing stress may suggest a causal relationship. We know that increased production of the stress hormone cortisol can cause abdominal obesity. Smoking is also a cause of abdominal obesity in women, but this declined significantly between 1968 and 2004 in both the 38- and 50-year-old cohorts (Björkelund et al. 2008). We know that exercise can reduce abdominal obesity in women (Björkelund et al. 2000). Exercise at work did not decrease markedly between 1968 and 2004 and, as mentioned, the proportion of women who engage in leisure exercise has risen. So it is possible that the increased experience of stress is one reason why we now see a greater tendency to abdominal obesity in women aged 38 and 50, without at the same time seeing an increase in mean bodyweight, compared to 36 years ago. Since abdominal obesity is in itself a risk factor for diabetes, heart attack and stroke in women, this could in turn indicate that the increasing stress constitutes a health hazard.

Personality

The Prospective Population Study of Women in Gothenburg also contains interesting findings about whether the personality profile of women aged 38 and 50 has changed between the 1960s and the 2000s, and if so, how. That is, the study is comparing different generations of women aged 38 and 50. A person's personality is regarded as being stable throughout life, but if the environment also affects the type of personality a person develops while growing up, personality changes should be discernible at a group level when different generations of women are compared, because the

environment changes. The adolescent environment in particular has probably changed for the latest generations of women. In earlier studies, for instance, women scored lower than men for ‘dominance’ and higher for ‘need to care for others’ and ‘need to be helped and taken care of’. Now that women’s life environment is starting to look more ‘male’ through having a higher proportion of wage-earners and more financial responsibility, perhaps women’s personality profile has also changed from that of earlier generations?

In the PPSW study, the Cesarec–Marke Personality Schedule (CMPS) and Eysenck Personality Index (EPI) were used for personality testing. Comparing personality tests on women aged 38 and 50 in the 1960s with those of the same respective ages in the twenty-first century, preliminary data suggest that the personalities of middle-aged women have changed and become more like those of men, with signs of increased self-assurance and independence. At the same time, women have retained their need for close relations. The findings support the hypothesis that the environment has significance for personality, and that women’s increased self-assurance and access to education, jobs and personal income also appear to have been important for their personality development. Whether this in turn increases the individual’s ability to deal with stress, despite the fact that experiencing stress appears to be on the rise among women, will probably become visible as the health trend for women in Sweden evolves over the coming decades.

Nervous complaints and dejection

The possible link between mental state – for instance whether you are experiencing nervous complaints or feeling low – and health has also been investigated in the Prospective Population Study of Women in Gothenburg (Hange et al. 2009). A Swedish study based on Statistics Sweden’s national questionnaire surveys (ULF surveys) has previously shown a connection at the population level between the experience of nervous complaints and anxiety, and increased morbidity and death. We were able to confirm these findings in the PPWS study and show that this above all applies to women in the

38- to 50-year age group, and primarily relates to cardiovascular disease. We found no increased risk of cancer among women who reported nervous complaints and/or dejection, but we did see a clearly increased risk of cardiovascular disease over a 32-year follow-up period which was especially pronounced in women aged 38 and 50, less so in women after menopause.

We still do not know whether measures that decrease the experience of nervous complaints and dejection reduce the risk of cardiovascular disease, but we do know that societal measures that lead to better socioeconomic conditions can reduce the risk of cardiovascular disease in women as well as men.

Similarities and differences

Cardiovascular disease is a group of illnesses where certain types of stress are believed to contribute to the development or worsening of symptoms. Myocardial infarction is the most common serious cardiovascular event in both men and women, although women tend to be affected later in life than men. In the WISH study, data from a large population study – Intergene – were used to compare which symptoms were most prominent in women and men when they had their first heart attack (Berg et al. 2009). While the understanding of differences – and obviously also similarities – between men and women in terms of symptoms, onset, risk factors and illness experience has grown in recent decades, there are many aspects of this field that remain to be studied and where more knowledge is needed.

This study included 225 persons, 52 women and 173 men (Berg et al. 2009). All the symptoms reported by this cohort in association with the onset of myocardial infarction were studied and registered. In both sexes the most common initial symptom was chest pain, which was reported by 89 per cent of women and 95 per cent of men. However, besides chest pain, more women also had symptoms such as nausea (approx. 50%), back pain (42%), dizziness (17%) and palpitations (11%). By contrast, there were no differences

between the sexes in terms of arm, shoulder, neck or jaw pain, cold sweats, dyspnoea, fatigue, stomach pain, vomiting or fainting. A higher proportion of women (71%) than men (48%) reported more than three symptoms.

To summarise, then, we can see that both men and women often experience chest pain when developing their first heart attack, but that it is more usual that women also report nausea, back pain and palpitations, and more often have several symptoms at the same time.

What promotes well-being?

It is hard to tell whether the favourable signs we see – i.e. the health trend in women as measured in terms of rising average lifespan and reduced risk of cardiovascular disease, as well as the significant decrease over the last 30 years in major unhealthy living habits such as smoking – will be able to offset what we believe to be negative signs, such as the rising experience of emotional stress among women of today. What do we know about making women feel well?

In the PPSW study, women who exercised during their leisure time were studied on the basis of their self-assessed health and well-being (Blomstrand et al. 2009) – a study that covers a 32-year span. The study shows a strong association between leisure exercise and how women describe their health and well-being. Not only did women who increased their leisure exercise experience improvement in their perceived health; those who exercised also rated their health as better than those who did not exercise, for both the short and the long term. Exercise was defined as more than four hours of walking, cycling, gardening or similar per week, i.e. just over half an hour per day.

Yet another study based on existing population studies in Gothenburg within the WISH project concerns the development of dementia in women. The study explored how different types of alcohol, and the consumption of spirits, wine and beer, are associated with the risk of developing dementia. Findings showed that moderate consumption of alcohol – but only in the form of

wine – was associated with a lower risk of developing dementia, while consumption of beer and spirits had no such protective effect (Mehlig et al. 2009).

A study of dental health and whether it influences the risk of coronary artery disease in women shows no significant link between periodontitis – inflammation of the gums – and coronary artery disease in women. The proportion of missing teeth, on the other hand, shows a strong association with coronary artery disease (Stenman et al. 2009). It is likely that factors behind toothlessness, such as socioeconomic conditions, also represent strong risk factors for heart disease in women. Good dental health also appears to create conditions for better general health.

What do the results tell us?

Drawing together the findings of the different research groups, the increased experience of emotional stress and anxiety stands out as one of the strongest negative trends for women's future health. The positive effects of social development on the health of the nation appear not to have benefited women to the same extent as men. We can also confirm that many signs that women have been making active lifestyle changes, with increased exercise, better nutrition and less smoking, even though the proportion of working women – some with two jobs – has increased over the last thirty years. It is fair to say that individuals have taken their share of responsibility for their health – but has society done the same? According to the studies, only half of today's middle-aged women rate their health as good! Women who report good health also report a higher degree of balance and manageability in their daily activities. They also report more satisfaction with their lives and less experience of stress, irrespective of socioeconomics and age.

One-quarter of middle-aged women report a high stress level and a low degree of influence on their work, while nearly 35 per cent state that their job encroaches on their leisure. The primary reason given for the high degree of experienced stress is lack of clear organisation and conflicts at work coupled with little opportunity to

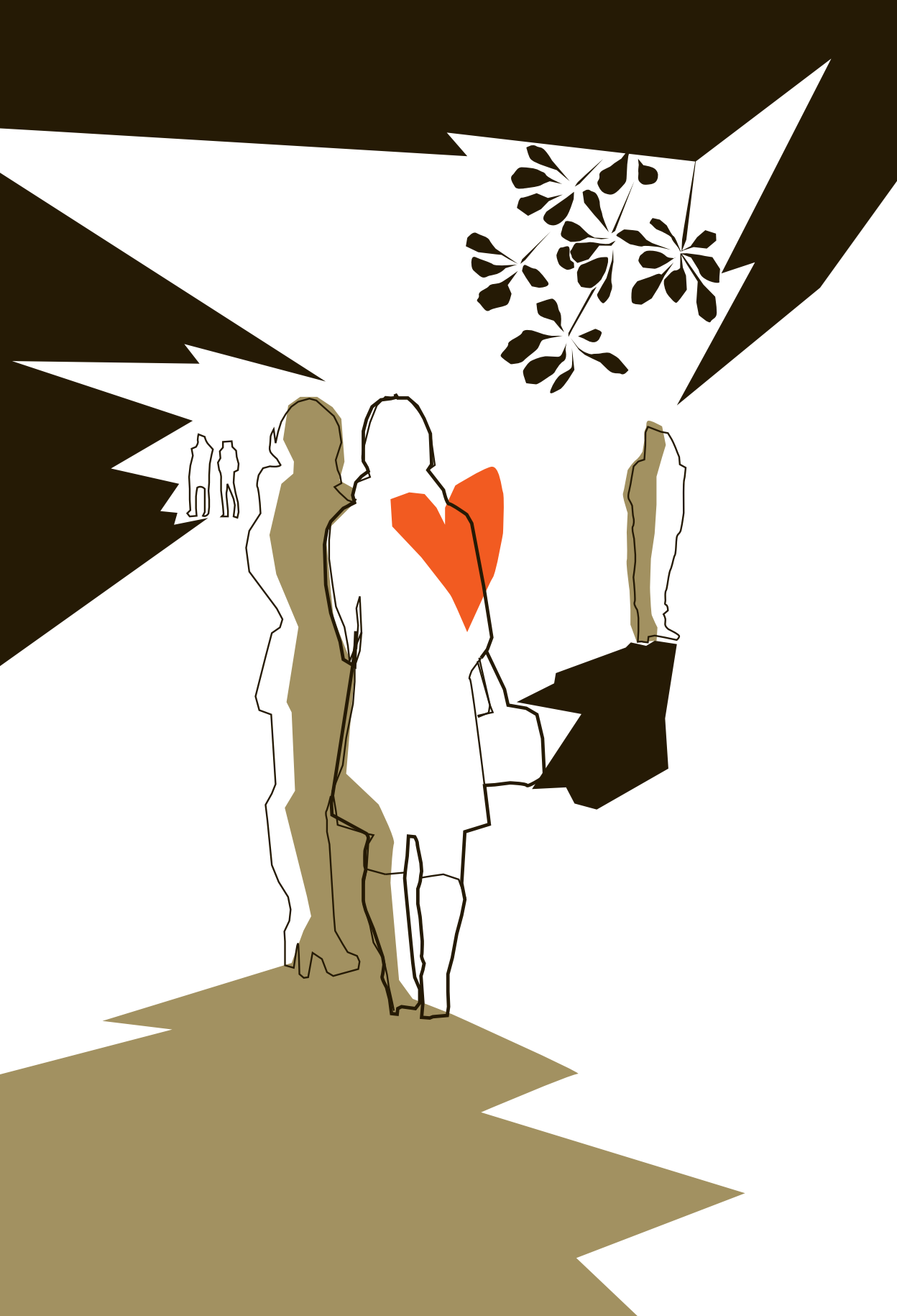
influence their work. This is also cited by women aged 38 and 50 as the leading reason for sick leave.

Overall, the studies should provide a basis for the assertion that society should make a great effort to give women better opportunities of influencing their living environment, their work, and their physical and mental working environment. Society should support women in their individual development and determine what society has to do in order for women to experience a balance between family, work and the individual. In particular, society should also focus on supporting women who are already known to be at higher risk of ill health, such as women in socioeconomically vulnerable categories.



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Why do women live longer than men? – a gender analysis of public health research

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Why do women live longer than men, while at the same time being in some respects more ill than men? This is the main question of this chapter, which will analyse mortality and morbidity among women and men in public health research and possible explanations from a gender theory perspective.

That women have a longer lifespan on average than men is not a law of nature, as we will show both in historical and geographic examples and in relation to age and social background. Let me start with a brief introduction as to why a gender theory perspective is necessary within public health science.

A gender perspective is needed in this area for several reasons. Firstly, attention to and knowledge about gender-related living conditions and their consequences for health are required if public health research is to develop in a way that will improve the health

of both women and men. Although gender research has long been regarded as a purely female concern, theory development has increasingly led the focus of analysis to shift onto relations between women and men. As a result, men's health and living conditions also have to be problematised.

Secondly, a gender perspective in the public health area can also lead to previously hidden questions, especially concerning gender-related power, being brought into the open. The theory development has given power perspectives a central position in gender research within public health science, resulting among other things in growing attention to the health consequences of men's violence against women. In the latest public health policy report from 2005, for instance, the Swedish National Institute of Public Health suggested that eliminating men's violence against women should become an objective within public health policy. Knowledge of gender theory is also necessary to prevent outdated ideas about women and men from being formed and becoming entrenched.

Thirdly, a gender perspective in the public health area may reduce the risk of exaggerating the differences between women and men, in that variations among women as a group and among men as a group are analysed in relation to other power dimensions such as socioeconomic status, ethnic background, sexuality etc. There is a growing movement in medical research that focuses on identifying and creating differences between women and men. Although this research trend has been sharply criticised for creating and exaggerating differences, the difference message is being put about in both scientific and popular science contexts.

New approach

The well-known Australian gender theoretician Raewyn Connell's theory about gender order can be seen as a new approach to understanding the health of women and men. According to this theory, every society can be characterised by the structurally organised relations between women and men which deal primarily with the distribution of power and control, of production (both

wage earning and work in the home) and of emotions and symbols. Analysis of gender relations in relation to health involves analysing how these gender relations are embodied as various problems of ill health.

Connell's theory on gender relations in the distribution of power can be used to explain women's poorer living conditions (in working life as well as the domestic situation) and how men's greater degree of power relative to women can lead to men's violence against women. Analyses of society's gender-related power order, such as the significance of gender-segregated working life for health, are of major importance in the public health area. The symbolic representation of relations between women and men for instance in the media may be a contributing reason why women are more affected by problems linked to the Western slimness ideal, such as eating disorders, while the dominant masculinity in our society is to a greater extent associated with abuse of alcohol, drugs and anabolic steroids as well as aggression, dominance, competitiveness and violence.

An advantage of the gender relations theory is that it also systematically analyses relations among men as a group and among women as a group in relation to power dimensions such as social and ethnic background and sexual orientation.

Researchers' explanations of the differences

Explanations for differences in mortality and morbidity between women and men that have been discussed in the scientific literature can be divided into two main types of models: (a) the biomedical model, which emphasises differences between the sexes in their biological constitution in terms of genes, hormones, physiology, and so on, which can lead to different risks of ill health; and (b) the sociocultural model, which is based on differences between the sexes primarily with regard to health-related behaviours and living conditions, such as conditions in working life and family life and other socially mediated factors that may represent health hazards.

Strong criticism has arisen in gender research against the sharp distinction made in medicine between the biological/genetic model on the one hand, and the sociocultural model on the other. Gender research also criticises the tendency within medicine to regard biological differences as primary and unalterable. Sociocultural conditions also influence apparently strictly biological factors such as stress hormones, blood pressure, muscle mass, bone structure, immune system, body shape etc. It is therefore important to problematise the view of biological sex differences and to analyse the interplay between social and biological conditions.

Average lifespan

Average lifespan from a historical perspective. In 2006, the average lifespan in Sweden was 83 years for women compared to 79 years for men. Women have not always lived longer on average than men in our country. In the hunter societies of former times, women died at an earlier age than men. This was not because women had a high rate of mortality associated with pregnancy, although they did, but because girls were undervalued by society. It was the boys, the future hunters, who had to be fed right. Girls fell victim to malnutrition and infectious diseases. The situation of girls changed in the farming society, but it was not until in the Middle Ages that the differences in mortality started to even out in Europe.

A diagram of the average lifespan of women and men in Sweden since 1750 shows an essentially unbroken rise in average lifespan for both women and men throughout this period. During this time, the average lifespan has more than doubled. The difference in average lifespan between women and men has fluctuated significantly over the period, from a maximum of six years longer for women in the late 1990s to a minimum of about two years longer in the 1920s. Until about 1830, average lifespan increased more for women than for men. The differences between the sexes then essentially diminished steadily until the 1920s, when the trend reversed and the gap started to widen quite steeply. Since the early 1990s the curve has turned: women's advantage in years is diminishing.

Various reasons for the difference in average lifespan between women and men have been discussed. Urban Janlert, who analysed gender differences in average lifespan in relation to certain cornerstones of Sweden's equality policy, points out that at a time when nothing much was happening in terms of equality policy, in the latter part of the nineteenth century, gender differences in average lifespan diminished. During the first half of the twentieth century, there was a 'social policy thaw' of great significance for equality in Sweden. The years 1925–1949 also saw the greatest increase in average lifespan for women relative to men during the whole of the period studied. Although no associations can be proven in Janlert's analysis, one interpretation is that measures which strengthen equality may have significance for increasing women's average lifespan. A central question here is obviously how long it takes for equality policy measures to have any visible impact on mortality rates.

In an analysis, Sam Willner has drawn attention to the importance of Sweden's alcohol policy for gender differences in mortality from a historical perspective. He suggests that changes in alcohol policy – which influence consumption levels as well as the prevalence of alcohol-related injuries – has had a greater impact on mortality among adult men than adult women because alcohol consumption is so closely linked to the dominant masculinity ideals in our society. The very liberal alcohol legislation introduced in 1809 led to a strong rise in aquavit consumption among men. This in turn caused the difference in average lifespan between women and men to increase until the mid-1850s, while the aquavit legislation of 1855 and the subsequent Bratt passbook system together with restrictions during World War I were important reasons for the drop in male excess mortality until the 1930s. According to Willner, the primary reason why gender differences in mortality then increased – particularly after 1950 – is the major rise in cardiovascular disease among middle-aged men as a result of changed eating habits and smoking. But Willner also believes that the liberalisation of alcohol policy – and resulting rise in alcohol consumption – has been

important for the rising excess mortality among men. Since Sweden joined the EU, alcohol consumption has increased significantly among both women and men.

Average lifespan in a global perspective. An overview of differences in average lifespan between women and men in 170 countries shows distinct variations between countries.

In some south-east Asian countries, average lifespan is fairly similar for women and men. Until a couple of years ago, the average lifespan was actually longer for men than women in some of these countries. The cause of women's higher mortality is not only frequent childbirth with reproductive complications, but also discrimination in the form that, for instance, girls have poorer access to food and healthcare and are forced to work instead of going to school. These countries are thus characterised by strong repression of women.

The opposite applies in countries where women's average lifespan is up to twelve years longer than men's (Russia and the Baltic countries). With the fall of the Soviet Union in the early 1990s, alcohol-related mortality quadrupled in Russia within a few years. Men of working age represent the largest share of alcohol-related deaths, and men's average lifespan fell by six years between 1990 and 1994. The high alcohol consumption among Russian men is a very important part of the explanation of the gender differences in average lifespan. In 2004 the average lifespan in Russia was 59 years for men compared to 72 years for women. The reason for these large gender differences is therefore the high mortality among men, rather than that women live longer than in other countries. The rising alcohol-related mortality in Russia and the Baltic countries can be linked to the profound changes which took place there at the political, economic, social and ideological level, with rising unemployment, increasing poverty and a higher divorce rate combined with increasing access to alcohol.

Mortality in relation to education. The 2005 Public Health Report charts the expected remaining average lifespan for women and men from age 30 distributed by the highest completed education level in the period 1986–2007.

The report shows that education-related differences in average lifespan increased particularly among women between 1986 and 2007. During this period, the difference in remaining average lifespan at age 30 increased from 2 years to 4.5 years in women, and from 3.4 years to 4.9 years in men. Highly educated men have a longer remaining average lifespan at age 30 than women with only a basic school education.

Mortality in different age groups and diagnoses. The ratio between women's and men's average lifespan has thus varied historically in Sweden. However, there are also tangible age-related differences in mortality. The higher mortality of men compared to women in relation to age group can be described as the quotient between men's and women's death rates in different age groups. If mortality is equal in men and women, the figure is one. If men have a higher death rate than women, the figure becomes greater than one. Statistics from 2003 show the mortality risk to be 1.3 to 3 times higher in men than women at all ages. At higher ages, the differences diminish. In the 20- to 24-year age interval, mortality is three times higher in young men than young women. The smallest difference between the sexes is seen during the teenage years and after age 85.

What is the reason for the high excess mortality among men? And why is the excess mortality highest in early adulthood? One way to study this question is to analyse mortality in different diagnoses, which can be done by calculating the number of years lost. The method of calculating years lost was developed to visualise mortality in younger age groups based on the fact that more years are lost if a person dies at age 20 than, for instance, at age 75. It assumes that a cohort of women and men will live between 1 and 74 years and computes the number of years lost for different diagnoses in women compared to men up to age 74.

Statistics in the 2005 Public Health Report show the number of years lost in different diagnoses in the 1- to 74-year age interval per 1,000 persons during a five-year period. Up to age 74, men lose more years than women in all disease groups except cancer. The greatest difference between women and men is seen in cardiovascular disease and trauma. However, one criticism of this type of calculation is that since women's average lifespan is longer than men's, the age interval used in the calculations should be longer for women than for men. Total mortality in cardiovascular disease is equal in women and men, while age-standardised mortality in cardiovascular disease is higher for men than women. The reason for this gender pattern is that women develop cardiovascular disease 8–10 years later than men. While sex hormones, especially oestrogen, are believed to protect women from cardiovascular disease, oestrogen medication provides no protection.

The diagnoses responsible for the excess mortality in young men aged 15–24 relative to young women are suicide and accidents.

Health habits. Differences in health habits between women and men are also important for male excess mortality. For a long time men used to smoke more, but they were overtaken in the statistics by women some ten years ago. Men also consume considerably more alcohol and have poorer eating habits than women. In Sweden, it has been estimated that alcohol consumption was responsible for 15–20 per cent of excess male mortality compared to women in the period 1945–1992, while 14 per cent of excess male mortality in the period 1985–1989 has been ascribed to smoking.

The 2009 Public Health Report provides data on the number of alcohol-related deaths in women and men. The report shows alcohol-related mortality to be considerably higher among men than women, particularly in the 45- to 64-year age group. In this age group, mortality fell among men but rose slightly among women during the 1970–2006 period.

Reports from the USA as well as Sweden show that at least one-third of the excess mortality in men over women is caused by

accidents, suicide, liver cirrhosis and respiratory disease. Much of this mortality is due to behaviours that in our cultures are more accepted among men, such as competitive performance behaviour, risk taking (especially in road traffic), acts of violence and high alcohol consumption.

If men were to modify their high-risk behaviour, their excess mortality could be significantly reduced. Similar Swedish calculations have produced the same findings. To speak only about behaviour modification is nevertheless too simplistic. The cause of behaviours has to be analysed from a social perspective based on relations between women and men as well as the significance of social and ethnic background.

Connell's theories allow us to understand differences in health between women and men as a result both of gendered living conditions and gendered practices, such as health habits.

In recent years, masculinity researchers around the world have problematised the higher mortality and inferior health habits of men (compared to women). Hegemonic masculinity is seen by Raewyn Connell as a masculinity ideal which in many societies is culturally dominant over other masculinities (such as homosexual masculinity) as well as all forms of femininity. Hegemonic masculinity in today's USA tends to be represented by white, well-educated heterosexual men with conditions such as high status, sexism and independence being important components.

Masculinity researchers suggest that health-related perceptions and behaviour are one way of demonstrating, respectively, femininity and masculinity. The dominant form of masculinity in our society is associated with greater risk taking, such as more hazardous health habits (e.g. high alcohol consumption and taking risks on the roads) and reluctance to seek medical care. High alcohol consumption can be a way to demonstrate power, thereby giving expression to the dominant masculinity.

Morbidity. The fact that women on average live longer than men while also being shown in several studies to have higher morbidity is sometimes called the medical paradox. However, there is a tendency to exaggerate the differences in morbidity between women and men by representing women's ill health as being so much worse than men's. Data from the ULF survey, conducted by Statistics Sweden (SCB) and reported in the 2009 Public Health Report, show for instance that there is no major difference between women and men in terms of self-reported health. There are on the other hand time changes and age differences. About 80 per cent of young women and men assess their health as good, compared to around 70 per cent of the older age group. Age differences diminished in the 1990s as a result of poorer health among younger people.

Allergic disorders are most common in boys until puberty, and then become more common in girls/women. Women are affected more often than men by immunological dysfunctions, such as autoimmune diseases. The reasons for these differences are not fully known, but hormonal explanations have been proposed with respect to allergy. One explanation sometimes offered for immunological diseases is that women have a more robust immune system than men. While a woman's more intensive immune system may result in sufficient protective antibodies being transferred to the fetus during pregnancy, the risk of certain autoimmune diseases also increases.

According to the 2005 Public Health Report, women have higher morbidity than men in three major diagnostic areas: urinary and reproductive diseases, musculoskeletal disorders and mental ill health. The ULF surveys for instance chart the development of mental ill health in young women and men since the late 1980s. The time differences are considerably greater than the differences between young women and men. Mental disorders have risen sharply since the late 1980s, especially in young women. Men on the other hand have a higher risk than women of primary tumours, overweight, diabetes, cancer diagnoses (after age 60) and alcohol-related morbidity as well as injuries and accidents.

Let us take overweight as an example. In the last twenty years, the incidence of overweight and obesity has risen. The increase gained pace in the early 1990s and is greater among men than women. The incidence moreover rises with age, even though overweight/obesity in recent decades has increased most among persons under 50 years of age. Half of all men, compared to one-third of all women, are overweight or obese. Obesity is on the other hand equally common in women and men, the proportion of obese individuals having doubled from 5 to 10 per cent between 1980 and 2005, according to the 2009 Public Health Report. Overweight and obesity are most common in lower social categories and among those with less education.

Explanation models for the higher incidence of musculo-skeletal disorders and mental ill health in women

The majority of diseases and symptoms are thus not most common in women. Below I will primarily discuss two diagnoses where women report more ill health than men.

The 2005 Public Health Report states the reasons for women's higher musculoskeletal morbidity compared to men as a combination of biological and sociocultural circumstances: less muscle mass, a gender-segregated labour market where women have more monotonous job tasks and poorer career opportunities, and women's double work burden with the main responsibility for home and family.

The gender-segregated labour market places women and men in different positions and different sectors within the labour market with far-reaching consequences for working conditions, economy and state of health. Women primarily have public sector jobs in healthcare, education and social care. Wages, wage development and opportunities for advancement are poorer in female-dominated jobs, one outcome being that women's aggregate lifetime earnings are much lower than men's. According to Statistics Sweden, women in 2007 earned 83.7 per cent as much as men when women's and men's wages throughout the labour market were compared. When age,

working hours, sector, education and occupation were taken into account, women's wages (in 2007) corresponded to 93.5 per cent of men's. However, several of these factors (particularly women's main responsibility for domestic chores, which means that they more often have part-time jobs) are strongly linked to women's and men's different living conditions. The greatest gender differences in standardised wage levels are seen in the private sector (91%), followed by the government sector (93%) and county councils (94%), while the least wage inequity is seen in the municipal sector, where women earn 98 per cent of men's wages.

Wage discrimination has a negative impact on women's careers and ability to earn a living. Financial stress has been shown to be an important factor giving rise to ill health that is more common in women than in men.

In addition, the labour market is generally less diversified for women. This can be an obstacle if you need to change your job because of ill health or in connection with long-term sick leave. A specific feature of male-dominated jobs is the high risk of injury in conjunction with workplace accidents. More gender research is required to shed light on the consequences of a strongly gender-segregated labour market for health and the work environment.

Mental health differences between women and men primarily relate to anxiety and depressive disorders. According to the 2005 Public Health Report, the gender differences are largely caused by men using alcohol to 'medicate' these complaints and therefore being seen primarily as alcohol abusers. Men are also over-represented in terms of completed suicide.

A 2004 report from the Swedish Council on Health Technology Assessment (SBU) concludes that the reasons for women's excess morbidity in depression are not fully known. However, the biomedical model cannot explain why the risk of depression is higher in women than in men. It is believed that sex hormones most likely have some effect, albeit less than the effect of environmental factors, while genetic factors appear not to explain the gender differences. Environmental factors brought out in the SBU report primarily relate

to inequitable living conditions, with women being disadvantaged not only in working life but also during their leisure time and in the home.

An increasing body of research points to the significance of the ‘double burden’, as well as other equality issues in couple relationships, to explain the higher incidence of depression in women. In her dissertation, Anna Månsdotter for instance showed in a study of 100,000 women and men who had their first child in 1978 that mortality was 25 per cent lower in men who took 30–60 days of parental leave compared to men who did not take parental leave. The study was controlled for income and socioeconomic position, but further research that also takes baseline health status into account is required in this area. A possible explanation for the findings could be that men who have responsibility for their children become less inclined to take risks, for instance on the roads, and more inclined to lead a healthy life. Another possible explanation is that men who take parental leave also increase their share of domestic chores (cleaning, cooking, washing up etc.), which takes some of the burden off the women in these relationships and thereby improves their health situation.

Men’s violence against women represents an extensive equality and public health problem. Medical gender research has been critically important in highlighting the significance and health consequences of the violence and assaults to which women are subjected above all by their spouses, cohabitees and other men around them. The physical consequences include everything from various injuries (internal injuries, fractures, burns, head injuries, vision and hearing injuries) to chronic pain, hypertension and cardiovascular disease. A woman’s heart disease may consequently have been caused by abuse. The psychological consequences of abuse include not only depression, but also sleeping problems, anxiety disorder, self-destructive behaviour, substance abuse and suicide. The reproductive complications are pregnancy, sexually transmitted diseases (including HIV), abdominal injuries, miscarriages, low-birthweight babies and premature births.

The perceived threat of violence also constitutes an extensive public health problem. Findings from the 2006 national public health survey show that 40 per cent of women and 10 per cent of men have refrained from going out alone due to fear of attack.

Although men's violence against women is an extensive public health problem, it has remained invisible both in medical research and training and in the interface between doctors and patients.

Unequal life circumstances emerge even during childhood, with girls for instance helping out more at home than boys. A study of 10- to 18-year-olds shows that 33 per cent of girls compared to 24 per cent of boys cook at least once a week. At the same time, more is invested financially in boys, both by individual families (toys, sports equipment etc.) and society (opportunities for sports etc.). Extensive Nordic educational gender research has shown that girls and boys are treated differently at school. Boys today still get more of both speaking time and physical space at school. The tendency for boys to dominate over girls in school also persists, although girls are finding new action patterns. Although the health significance of these and other unequal conditions of life in childhood has been demonstrated, more research is needed.

Yet another common explanation model for women reporting depressive symptoms more often than men is based on the premise that gender differences in ill health are due to men's ill health being missed because of gender bias in the measuring methods (a so-called artefact). In various studies, certain rating scales such as HADS (the Hospitality, Anxiety and Depression Scale) have shown minimal gender differences with respect to depression and anxiety. Help-seeking behaviour has also been cited, especially men's reluctance to seek medical care. The SBU report nonetheless suggests that the gender differences cannot be explained by measuring errors.

Criticism of difference research

The growing interest in gender differences – whether biological or social – in medicine and society carries the risk of focusing on the differences while ignoring the similarities between the sexes. There

is also a risk of essentialism – a tendency to regard differences between women and men as constant and unalterable. It is above all biomedical research on differences between women and men that has been sharply criticised for leading to the view that men and women are two separate biological groups, and for biological gender differences increasingly being taken for granted. But the sociocultural explanation model also has a tendency to assume that differences between women and men apply regardless of time, place or culture. The risk of essentialism is obvious when sex/gender differences are uncritically generalised as applying to all women and men with no analysis of intra-group differences or varying sociocultural conditions. This also creates the risk that intra-group differences among women and men relating to age, social and ethnic background as well as sexual orientation become invisible. Differences relating to social position, for instance, are often greater within women as a group, and men as a group, than between the sexes.

Gender difference research – for example focusing on men as the norm – can be a stage in the development of gender research. I have designed a model for researchers interested in developing gender research either from difference research or gender-blind research. The premise of the model is that gender research differs in several ways from difference research and gender-blind research. While gender research questions the existing knowledge view within medicine, difference/gender-blind research is conducted as part of the prevailing paradigm. While gender research draws attention to the importance of analysing gender from a structural perspective, in difference/gender-blind research gender is primarily used as a variable. The results will therefore differ. Difference research leads to more research of the same type, where knowledge about women is added to existing knowledge about men. By questioning the existing knowledge base, gender research – with its base in power analyses and theory development – can lead to entirely new knowledge about women's and men's health. Theories need to be developed which complement and contrast with the dominant positivist theory

that prevails within medicine. Within gender research, masculinity research contributes to a dynamic development of knowledge about men's health, while men become one of several variables within difference research.

Measures and research needed

Increased equality in health between women and men – which in our country includes a reduction in hazardous health habits among men and improved mental and physical health among women – requires at least two types of measures, according to Lesley Doyal. Firstly, structural measures are necessary to achieve increased equality between women and men in society, particularly in terms of power and influence, financial condition and work distribution. Although Sweden leads the world in the proportion of women in elected decision-making bodies, a 2003 Government publication suggests that there are many signs pointing to the persistence of discriminatory structures at every level. The Government commission report on women's power in society, *Kvinnomaktutredningen*, found that the welfare state strengthens the position of women. Women's financial dependence on men has diminished while their ability to support themselves and any children has increased. At the same time the welfare state rewards typically male behaviour and use of time in the sense that paid work is considered more important than unpaid work while many social transfer payments (unemployment benefits, sick pay, pensions) are tied to employment income. Since men are wage earners to a greater extent than women, they receive higher sickness benefits and pensions.

The other element highlighted by Doyal is policy measures that give women and men greater freedom to create gender themselves in relation to society's dominant perceptions of masculinity and femininity. She mentions education strategies as well as more flexible employment conditions and changes to the social insurance structure that would give women and men better opportunities to open up and change their lives compared with society's expectations and norms for men and women respectively. Anna Månsdotter has used Swedish

data to show that the longer parental leave fathers take, the lower their risk of premature death. As mentioned above, the mechanisms behind this could relate to a change in masculinity among fathers who are home with their child which reduces their risk taking and increases their focus on social care – which in turn may lead to better health habits and lower mortality. Månsdotter's findings support Doyal's hypothesis about the importance of structural changes to the gender order (in this case the distribution of parental leave between women and men) for influencing the creation of masculinities that in turn are linked to state of health and mortality. The study was corrected for social background, but since it could not take selection mechanisms into account, there is a need for further studies in this area. (The methodological shortcomings of Månsdotter's study have been addressed in my own research.) Findings from the Luleå cohort – a group which has been followed through repeated surveys since class nine (c. 15-year-olds) in Luleå in 1981 – show that experiences of inequality in a couple relationship increase the risk of mental ill health both among women and men, even when their earlier state of health and social background factors are taken into account. Taking the main responsibility for the home and housework also increases the risk of mental ill health among women, but not among men.

There is a major lack of knowledge in Sweden about what part the creation of the dominant masculinity in our society has had to play in men's higher alcohol consumption, poorer eating habits, higher risk taking and higher mortality, compared to women. Most of the small amount of research that does exist in the area comes from Australia and the USA, countries whose gender regimes differ from the Swedish. For this reason we need not only more studies from Sweden, but also studies on different groups of men. We further need gender research on men's excess mortality in relation to age, including qualitative and quantitative analyses of why men's excess mortality is so high in the 20- to 24-year-old age group.

At the same time we must recognise that the focus on masculinities can result in knowledge about women's conditions of life and their health being overshadowed. On the premise of

Connell's theories about the significance of gender relations for health, it is important in closing to draw attention to the almost complete lack of research – both international and national – on the significance of different created femininities for women's health. From a salutogenic standpoint, the dominant femininity in society could be highlighted as a good example, as it generally shows less inclination to risk taking and a higher degree of health awareness compared to the dominant masculinity. The perspective of change is important here: for instance, on the significance of smoking in the context of creating a certain femininity, and why women for the last ten years have been smoking more than men. We consequently need research on the impact of both masculinities and femininities on health habits and state of health in different groups of people (relative to social and ethnic background, age, sexual orientation etc.) and in different contexts.

Current research project

FAS is funding the study 'Is equality in housework related to state of health? A 27-year follow-up of the Luleå cohort'.

The hypothesis of our study is that improved equality in couple relationships can lead to better health in both women and men. The reasons may differ for women and men. Increased equality can mean less time pressure for women as well as more responsibility and less risk taking among men.

The questions are:

1. Does increased equality lead to better health among women and men?
2. What are the potential reasons, i.e. what does increased equality mean for men's and women's health?

The study is based on the Luleå cohort, which consists of all pupils who attended class nine in Luleå municipality in 1981. The cohort has been followed through extensive questionnaire surveys (about state of health, health habits, labour market situation, social background, distribution of housework and parental leave etc.)

at ages 16, 18, 21, 30 and 43. The response rate is high – after 27 years, 94 per cent of those who attended class nine are still participating.

Quantitative methods are used to analyse question 1, while question 2 is analysed qualitatively. Interviews are conducted with a strategic sample of participants who have children. Printouts of the interviews are analysed using grounded theory. Equality in couple relationships has not previously been analysed to any significant degree in relation to potential health consequences. The study may therefore be of major significance for both public health work and clinical practice.



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From women's health to gender medicine

An anthology

Are older women given worse medical drugs than men? Do women suffer more easily from anxiety because of their hormones? Does smoking at the age of 20 affect the risk of developing osteoporosis later in life?

Many aspects of women's health are still unexplored territory. In this book, researchers talk about their exciting, new projects. The knowledge they uncover will help not just women. Men, too, can benefit from studies based on a gender medicine approach. Could it perhaps be true that men who live more as equals actually have better health?

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