CENTRE FOR
FERTILITY AND HEALTH

ANNUAL REPORT 2018

NIPH
Norwegian Institute of Public Health

Norwegian
Centre of
Excellence
The Research Council of Norway

CONTENTS

WELCOME FROM THE HOSTING INSTITUTION

CAMILLA STOLTENBERG DIRECTOR-GENERAL OF THE NORWEGIAN INSTITUTE OF PUBLIC HEALTH

As Director-General of the Norwegian Institute of Public Health, I am proud to welcome the Centre for Fertility and Health to our institute. The Centre is one out of ten Centres of Excellence awarded nationally by the Research Council of Norway in 2017 and the only one hosted by an institution outside the university sector.

The Norwegian Institute of Public Health is a national institution under the Ministry of Health and Care Services. Our vision is "Better health for all" and we are responsible for generating new knowledge in order to improve health in Norway and globally. To reach this goal we need rich national data and high quality research. To prevent diseases and promote health, we need more insight regarding causal mechanisms in disease aetiology, and must develop cutting edge methods that move these fields forward. Our new Centre of Excellence is a great asset to the institute in all these domains.

The marked changes in patterns of fertility and family structure observed over the past decades have large impacts on our societies. Some consequences of these changes are known, but most are unknown. The Centre has set out to unravel the health consequences of these fertility changes, using Norway's rich data from registers, health surveys and biobanks. The Centre will provide new knowledge in the scientific forefront and be useful for decision makers and other stakeholders in policymaking.

The institute provides infrastructure and facilities for the Centre. Fruitful synergies are reaped between the Centre and the other departments at our institute in the fields of genetics, epidemiology, mental health, toxicology and health services, and several seminar series have been established to promote scientific exchange. I am confident that the Centre will continue to develop strong collaborations with our other units and with scientists in Norway and abroad. To foster the Centre as an international research hub, we have provided the Centre with guest workspaces, where scientists can visit for shorter or longer periods to collaborate in ongoing projects and to develop novel ideas.

I have high expectations for the Centre. Since its inception in 2017, the Centre has hired excellent researchers, some with professorships at leading international universities, and attracted prominent international collaborators. The Centre has ambitious plans for expansion, and is active in applying for further funding from H2020, the Research Council of Norway and other sources. Such funding will provide new opportunities, and I am certain that the Centre will be a great inspiration for our research and make important scientific contributions over the coming years.

It is a great privilege to host the Centre at the Norwegian Institute of Public Health, and I am committed to secure its success.

Camilla Stoltenberg
Director-General

OVERVIEW

BY PER MAGNUS
CENTRE DIRECTOR

Dear friends, I am proud to present the first annual report from CeFH. The report sums up activities in 2018. It has been a wonderful experience to get started.

The first year

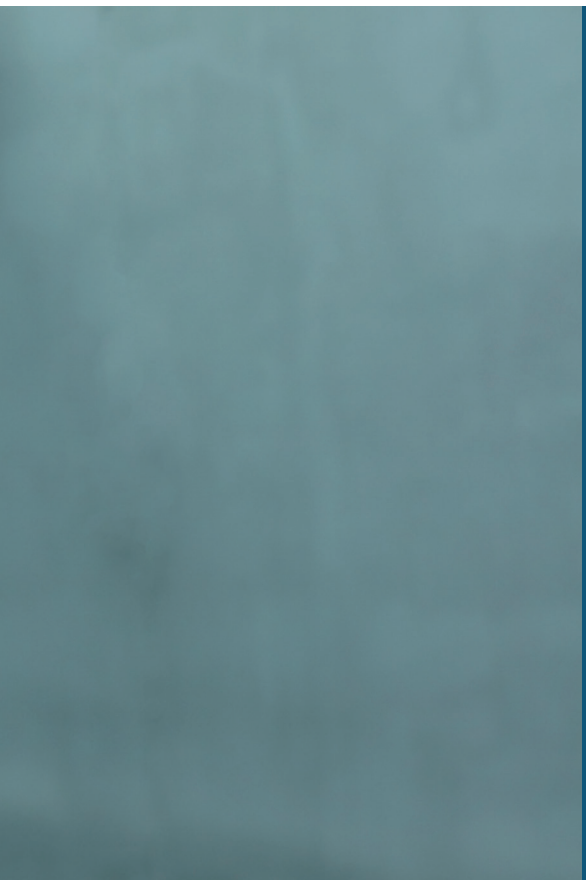
The Centre was established on November 1, 2017. During the past year, we have moved the themes in our application forward. In addition, valuable spin-offs and new ideas have emerged. One cannot put experienced and creative people in one place and expect them to follow a narrow path. Our project portfolio has grown. In some projects, we use data sets that are already established, whereas for others we are establishing new data sets. In 2018, many efforts have gone into planning and establishing these new data sets. Our host institute has provided us with office space, including workspaces for guests and collaborators. We have set up seminar series to foster scientific exchange. There has been more attention from public media than expected, as the decreasing fertility rate has sparked public debate. The government has given us the task to explain the causes of the decline during the coming year - a daunting challenge.

Staff and funding

By the end of 2018, 19 men and 16 women were formally associated with the Centre, including full-time researchers, researchers in part-time positions and foreign researchers with whom we have established collaboration agreements, and administrative personnel. In addition, the Centre collaborates closely with several other researchers in Norway and abroad at a number of reputable research institutions. In 2018, we hired four new researchers, and we have ambitious plans for continuos growth as new external funding is obtained.

Scientific output

The Centre has contributed in 62 scientific papers since it was established. 51 of these were published in 2018. They reflect our backgrounds in demography, genetics, statistical methods and epidemiology. We are increasingly seeing manuscripts with authors from different disciplines. We have, among other things, shown that the relationship between marital status and life expectancy has become stronger over the last decades; that investing in adolescents as the parents of the next generation is important for the well-being of both current and future generations; that children's age at the parents' divorce can affect anti-



depressant use in adulthood, and that children born after assisted reproduction have an increased risk of asthma. We have also contributed to the discovery of new genetic variants for ADHD. Researchers at the Centre contributed to more than 70 news reports in Norway in 2018, and have received international press coverage on selected publications. We have presented our research to other researchers, decision makers and other stakeholders at conferences and meetings in Norway and abroad.

Collaboration and networks

We have established collaborations with prominent international researchers in the field, including Allen Wilcox, Emily Grundy, Wendy Sigle, Eric Bonsang, George Davey Smith, Abraham Aviv, Ezra Susser, Hans-Peter Kohler, Mikko Myrskylä. To increase the recruitment of younger international researchers, we established "The Gro Harlem Brundtland Visiting Scholarship". This scholarship was announced and awarded to two young researchers from the University of Bristol, UK. Both use data from Norwegian registries and cohorts. In May 2018, the Centre organized an opening symposium. The aim of the symposium was to present the Centre's research agenda, to foster new research ideas and to establish and consolidate collaborations.

A promising future for the Centre

One challenge is to explain to some of our surroundings that we cannot answer all difficult questions immediately. This type of research takes time. We are, of course, harvesting some low-hanging fruits. But we are just taking the first steps on the paths into exciting research areas.

Per Magnus
Centre Director

HIGHLIGHTS 2018

Major publications

The increasing mortality advantage of the married: The role played by education. **Kravdal Ø**, **Grundy E**, Keenan K. *Demographic Research*. 2018;38:471-512

Adolescence and the next generation. Patton GC, Olsson CA, **Skirbekk V,** Saffery R, Wlodek ME, Azzopardi PS, Stonawski M, Rasmussen B, Spry E, Francis K, Bhutta ZA, Kassebaum NJ, Mokdad AH, Murray CJL, Prentice AM, Reavley N, Sheehan P, Sweeny K, Viner RM, Sawyer SM. *Nature*, 2018;554:458-466.

New evidence about effects of reproductive variables on child mortality in sub-Saharan Africa. **Kravdal Ø**. *Population Studies* 2018;72(2):139-156.

Maternal history of miscarriages and measures of fertility in relation to childhood asthma. **Magnus MC**, Karlstad Ø, Parr CL, **Page CM**, Nafstad P, **Magnus P**, London SJ, **Wilcox AJ**, Nystad W, **Håberg SE**. *Thorax* 2019;74(2):106-113.

Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. Demontis D et al. *Nature Genetics*. 2018;51:63-75.

Parent-of-origin-environment interactions in case-parent triads with or without independent controls. G**jerdevik M**, Haaland ØA, **Romanowska J**, **Lie RT, Jugessur A**, **Gjessing HK**. Annals of Human Genetics 2018; 82(2): 60-73.

Major events

Opening symposium
The inaugural symposium of the Centre was arranged on May 8 and gathered over 100 participants. The conference was opened by Linda Hofstad Helleland, Minister of Children and Equality, Camilla Stoltenberg, Director-General, Norwegian Institute of Public Health and Liv Furuberg, Research Council of Norway. The aim of the symposium was to present an overview of trends in fertility and family structure and good examples of research within the Centre's area (from several disciplinary angles), foster new research ideas and consolidate collaborations – within and between disciplines.

The Gro Harlem Brundtland Visiting Scholarship
The scholarship was announced in May 2018, and two researchers, Robyn Wootton and Gemma Sharp were awarded the grant for 2018 and 2019.

Recruitment
We hired four new researchers - Jonas Minet Kinge, Maria Magnus, Fartein Ask Torvik and Martin Flatø - adding to the team described in the application. They have complementary expertise in economics, epidemiology, psychology and demography.

Professor Susan Sawyer accepted our invitation to join the Scientific Advisory Committee.

New offices
The Centre personnel moved to new office spaces in June 2018.

We obtained funding for the projects:
"The intrauterine redox state and telomere length in the newborn", led by Håkon Gjessing and Astanand Jugessur.

"HEALTH-GAP. Health, maturity, and the gender gap in education", led by Camilla Stoltenberg, Fartein Ask Torvik and Martin Flatø.

"International Pregnancy Drug Safety Studies (InPreSS)", led by Kari Furu.

OUR RESEARCH

The scientific goal of the Centre is to greatly advance the understanding of how changes in patterns of fertility and family structure influence child and adult health through social and biological pathways. To reach this goal, the Centre has put together an international team including epidemiologists, geneticists, demographers, statisticians, and economists.

In this annual report, we describe our research in five integrated themes of research. We also present our key research projects. Most of our research projects and activities cut across several research themes.

Theme 1: Maternal and paternal age.
The impact of advanced maternal and paternal age at childbirth on diseases in parents and offspring.

Theme 2: Fertility problems.
Health consequences of subfertility and assisted reproductive technologies for parents and children.

Theme 3: Fertility and family structure.
Health consequences of other components of the reproductive history (number of children/siblings, childlessness, age at first birth, interval between births) and family instability.

Theme 4: Statistical methods.
Our research employs numerous statistical analysis strategies where we contribute actively to the methods development.

Theme 5: Intergenerational transmission of health.
How health and disease are transmitted between generations through biological and social pathways.

THEME 1

MATERNAL AND PATERNAL AGE

Parental age at first birth is increasing in most countries. For example, in Norway the mean age of mothers at first birth has increased from 23.3 years in 1970 to 29.0 years in 2016. The mean age of men at first birth has also increased (see Figure 1). At the same time, the total number of children born to each woman has declined across the world, and not only because of the later entry into motherhood. If we consider the development from a the perspective of the child, the average age of the child's parents at the time of birth has typically increased. One of Centre's goals is to add to the knowledge about how a higher maternal and paternal age affect pregnancy outcomes and children's health, through social and biological mechanisms.

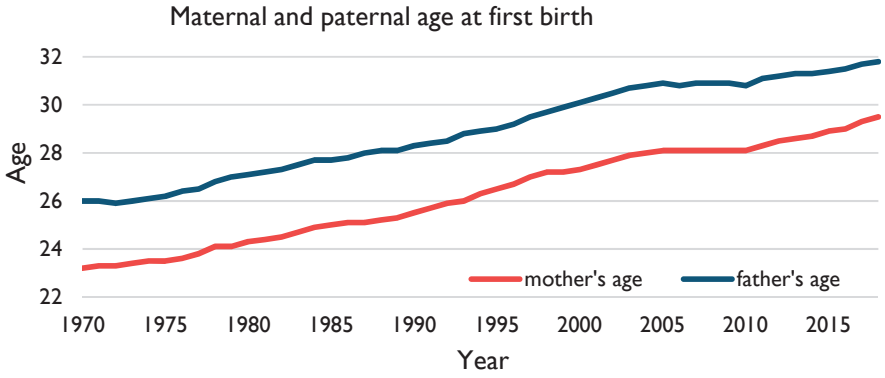


Figure 1. Mother's and father's age at first birth in Norway 1970-2018. Numbers in the period 1970-1985 are calculated with new data in 2009.
Source: Statistics Norway

Norway is an excellent venue to study this because trends are similar to those observed elsewhere in richer countries, and unique data collected in Norway enables detailed long-term prospective studies.

One of several possible biological mechanisms involves telomere biology. Our research on this topic is presented briefly below. The social pathways are also diverse. For example, one reason why parental age may affect child health is that older parents are likely to have more economic resources to spend on their children. They may also have accumulated more knowledge and may be more mature. On the other hand, they are less likely to survive until the child reaches adulthood. Another issue, addressed under theme 3, is that the age when a person becomes a parent (for the first time) has implications for his or her own health – through both biological and social pathways.

Telomeres and mitochondrial DNA

Several lines of evidence link telomere length to aging and longevity. Telomere length is highly heritable and largely determined at birth. It is therefore important to elucidate prenatal influences that affect telomere length in the newborn. A great advantage of the Norwegian Mother and Child Cohort Study (MoBa) is that we have access to DNA samples from mother-father-newborn trios, allowing us to analyse telomere lengths in a familial context to understand the association between parental age at conception and telomere length in the newborn, as well as other health outcomes such as neurodevelopmental diseases, cancer and cardiovascular diseases.

We have established a collaboration with key scientists at Rutgers University in New Jersey, USA, to specifically test whether associations between advanced parental age and health outcomes in children can be explained by telomere biology. Another research topic is the effect of mitochondrial genetics and maternal smoking during pregnancy on telomere length in offspring. Advanced maternal age is associated with increased occurrence of chromosomal abnormalities in offspring, increased risk of adverse perinatal outcomes, as well as diseases of pregnancy such as preeclampsia, which in turn is associated with

later cardiovascular disease.

The scientific work is organised in several projects. Two ongoing projects, "Telomere length, epigenetic age and T cells in women who give birth at an older age" and "Telomeres and women fecundity", were established before the Centre was formally started. A new project, "The intrauterine redox state and telomere length in the newborn" is being co-led by Håkon Gjessing and Astanand Jugessur who obtained funding from the NRC program Frimedbio in 2018. Researchers at the Centre are planning further research involving telomere length analysis in collaboration with Rutgers. The projects are planned to start in 2020.

The epigenetic clock and biological age

"Epigenetic clock" is a term used to describe a molecular marker of ageing measured by DNA methylation. DNA methylation measured in peripheral blood correlates closely - but not exactly - with chronological age. Recent research has shown that differences in methylation at a given chronological age is associated with a range of disease outcomes, and may provide a better marker for biological age that is independent of chronological age. We know that fertility declines with chronological age, but why does fertility vary so strongly among people of similar age? We will use DNA methylation to identify the role of biological aging in fertility and in disease development.

DNA methylation
DNA methylation is a process by which methyl groups are added to the DNA molecule. Methylation can change the activity of a DNA segment without changing the DNA sequence itself. Thus, DNA methylation plays an important role in the activation and silencing of genes.

Other projects

In 2018, we took part in a Nordic collaboration to study the effects of maternal age on children's birth weight using register data from Norway, Denmark and Sweden. This work will be presented at the annual conference of the Population Association of America in 2019.

In collaboration with Wendy Sigle at the London School of Economics, the first draft of a paper was written about how old mothers differ from old fathers in terms of social background and earlier childbearing history. Such knowledge about the characteristics of old parents helps us to understand what kind of factors one should consider when analysing implications of advanced parental age for child health.

Furthermore, in a methodological paper accepted in for publication in *Demographic Research*, we discuss an alternative to the commonly used sibling models when investigating effects of parental age. While our alternative approach also has some disadvantages, it can be useful when the intention is to delineate whether observed child health outcomes are effects of higher parental age or just effects of the child being born in a later calendar year.

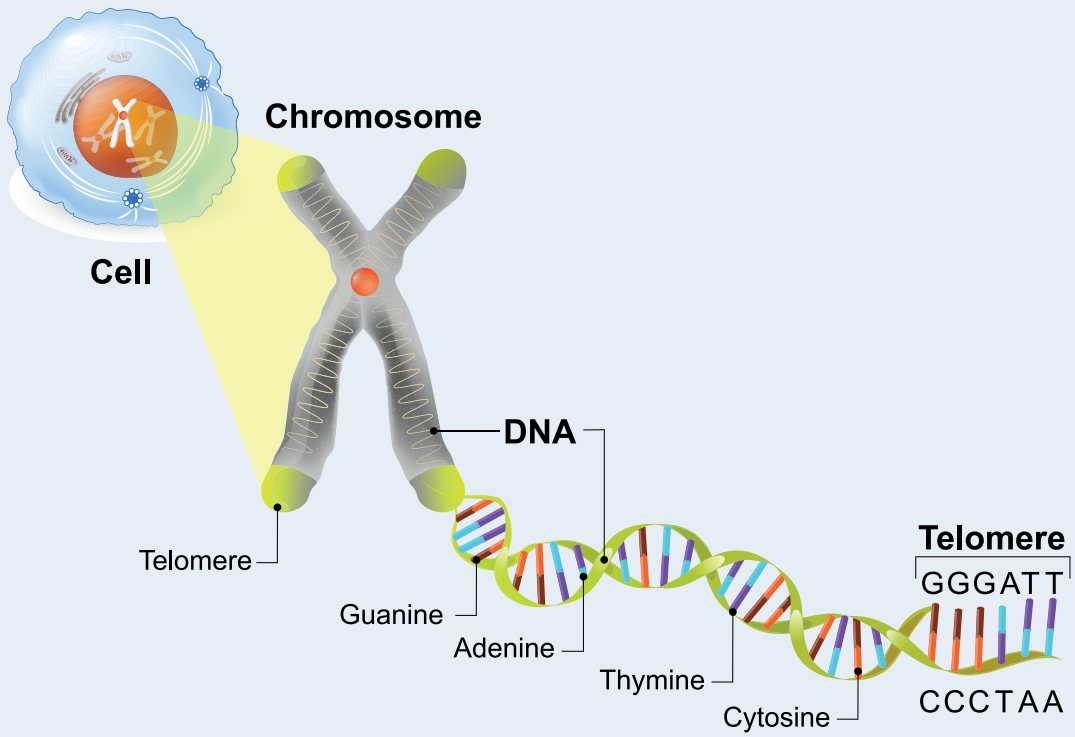


Figure 2. Telomeres are repetitive sequences of nucleotides (TTAGGG) at the ends of the chromosomes. They play an important role in protecting the ends of the chromosomes from deterioration. During cell division, the DNA is unpacked from the chromosome to allow replication. For each cell division cycle, the telomeres are shortened. Thus, the telomere length generally declines with age. However, male germ stem cells, in contrast to almost all other cells, exhibit progressively longer telomeres with aging due to telomerase activity. Furthermore, telomere length is heritable, and children of older fathers are born with longer telomeres. Telomere length is associated with several diseases including cancer, cardiovascular diseases and neurodevelopmental disorders. We will investigate the role of telomere biology in associations between parental age and disease. © *designua / Adobe Stock*

THEME 2

FERTILITY PROBLEMS

As mothers' and fathers' age at first birth have increased, we have also witnessed increased fecundity problems in the population. There has been a steady increase in the use of assisted reproductive technology (ART) since its introduction in Norway in 1984. Because the total number of births per woman has also decreased, the proportion of children conceived in this way has increased. Today, around 2500 children are born in Norway each year through ART, which is about 4% of all births, and around 7 million children have been born through ART worldwide. Moreover, as in other countries, there has been an increase in childlessness in Norway, from 10% in 1985 to 13% in 2015 for women and much more pronounced in men, from 14% 1985 to 23% in 2015.

Whilst most mothers treated with ART and children born through ART are healthy, there is some evidence pointing to adverse effects. ART has been associated with adverse pregnancy outcomes and increased risk of congenital malformations, infant morbidity and mortality. ART is also associated with several childhood diseases as well as cardiovascular diseases and cancer in mothers. One proposed mechanism for the detrimental effects of ART procedures is epigenetic modifications of the DNA during gametogenesis, fertilisation, and early embryonic development. However, it is not clear whether the observed adverse effects of ART are caused by the procedure itself or if it is caused by the underlying subfertility itself or higher age of the mother.

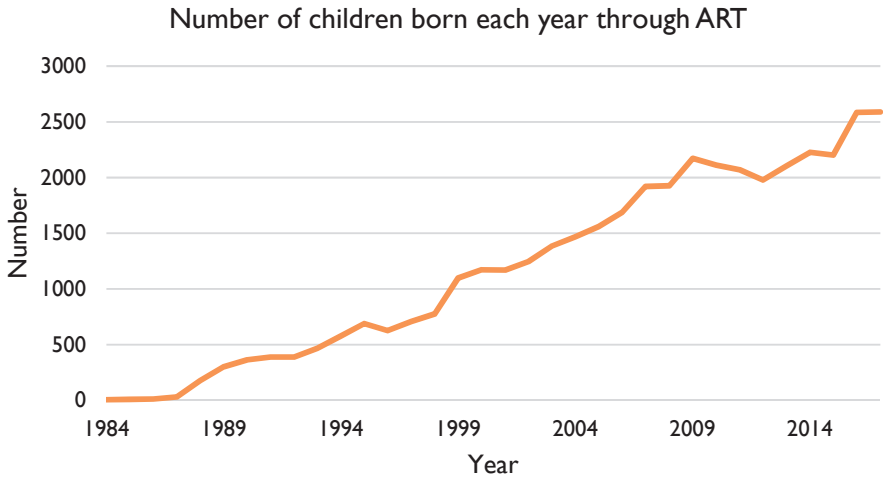


Figure 3. Number of children born through ART in Norway from 1984 to 2018. *Source: Statistics Norway*

We will estimate short and long-term health consequences of ART for women and offspring using a combination of data from registers, cohorts and biological samples. In particular, we are interested in health consequences of subfertility in women and men, and will examine epigenetic changes induced by ART, and determine their possible roles in diseases.

The START project

Our Centre of Excellence funding has permitted us to initiate an analysis of

Epigenetics

Epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. Epigenetics most often denotes changes that affect gene activity and expression, but can also be used to describe any heritable phenotypic change. Such effects on cellular and physiological phenotypic traits may result from external or environmental factors, or be part of normal developmental program. The standard definition of epigenetics requires these alterations to be heritable, either in the progeny of cells or of organisms. The term also refers to the changes themselves: functionally relevant changes to the genome that do not involve a change in the nucleotide sequence. Examples of mechanisms that produce such changes are DNA methylation and histone modification, each of which alters how genes are expressed without altering the underlying DNA sequence.
Source: Wikipedia

epigenetic signatures (e.g. DNA methylation) and potential epigenetic effects in subfertility and ART. For this, we have established a collaboration with Robert Lyle at the Norwegian Sequencing Centre. In 2018, we started pulling 6048 samples from the biobank of the Norwegian Mother and Child Cohort Study. The samples will be analysed for DNA methylation with the new EPIC array covering more than 850 000 methylation sites across the genome. The samples include 1000 trios of mother-father-children born after ART and 1000 control trios.

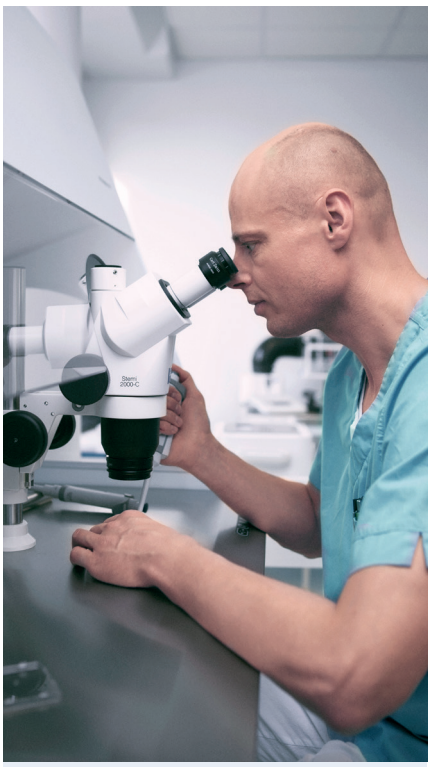
Metabolic profiles and perinatal outcomes

In collaboration with Debbie Lawlor at the University of Bristol, UK, we collaborate in the project "Prenatal metabolic profile and in vitro fertilization (IVF), pregnancy, perinatal and longer-term outcomes". The aim of the project is to compare metabolic profiles in couples (women and men) who conceive via IVF and determine if they can cause pregnancy/perinatal outcomes and if they can be used to predict outcomes. We will pull samples from 16 000 participants in the Norwegian Mother and Child Cohort Study in 2019 and analyze their metabolic profiles.

The ART register study

In "the ART register study", we combine Norwegian registry data to study causes and effects of subfertility and ART. This project is a collaboration with Allen Wilcox at the National Institute of Environmental Health Sciences, USA. We have also hired researchers in joint positions between our Centre and fertility clinics in Norway who contribute with their clinical experience and expertise in ART research. Our aim is to identify factors that affect fetal growth, gestational length and adverse pregnancy outcomes. We will compare pregnancies resulting from ART with those resulting from natural conception. In this project, we use data from various registries including the Medical Birth Registry of Norway, the Norwegian Mother and Child Cohort Study and the Norwegian Patient Register.

We have also started a descriptive analysis of the sociodemographic profile of children born after ART, with Alice Goisis at University College London, UK. A paper has been accepted for presentation at a conference in 2019.



Researchers at fertility clinics in Norway, such as Spiren Fertilitetsklinikk in Trondheim, contribute with their clinical experience and expertise in ART research.
Photo: Spiren Fertilitetsklinikk / Fotograf Hermstad AS

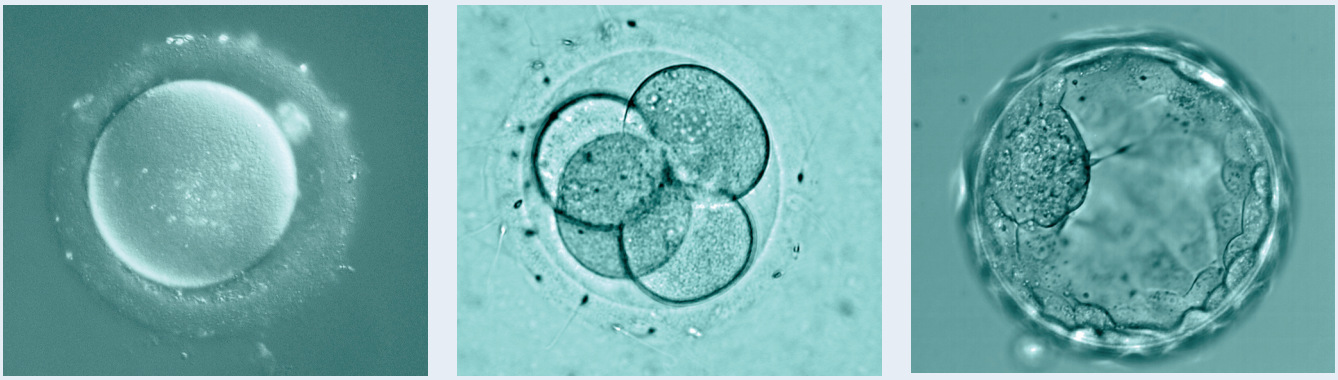
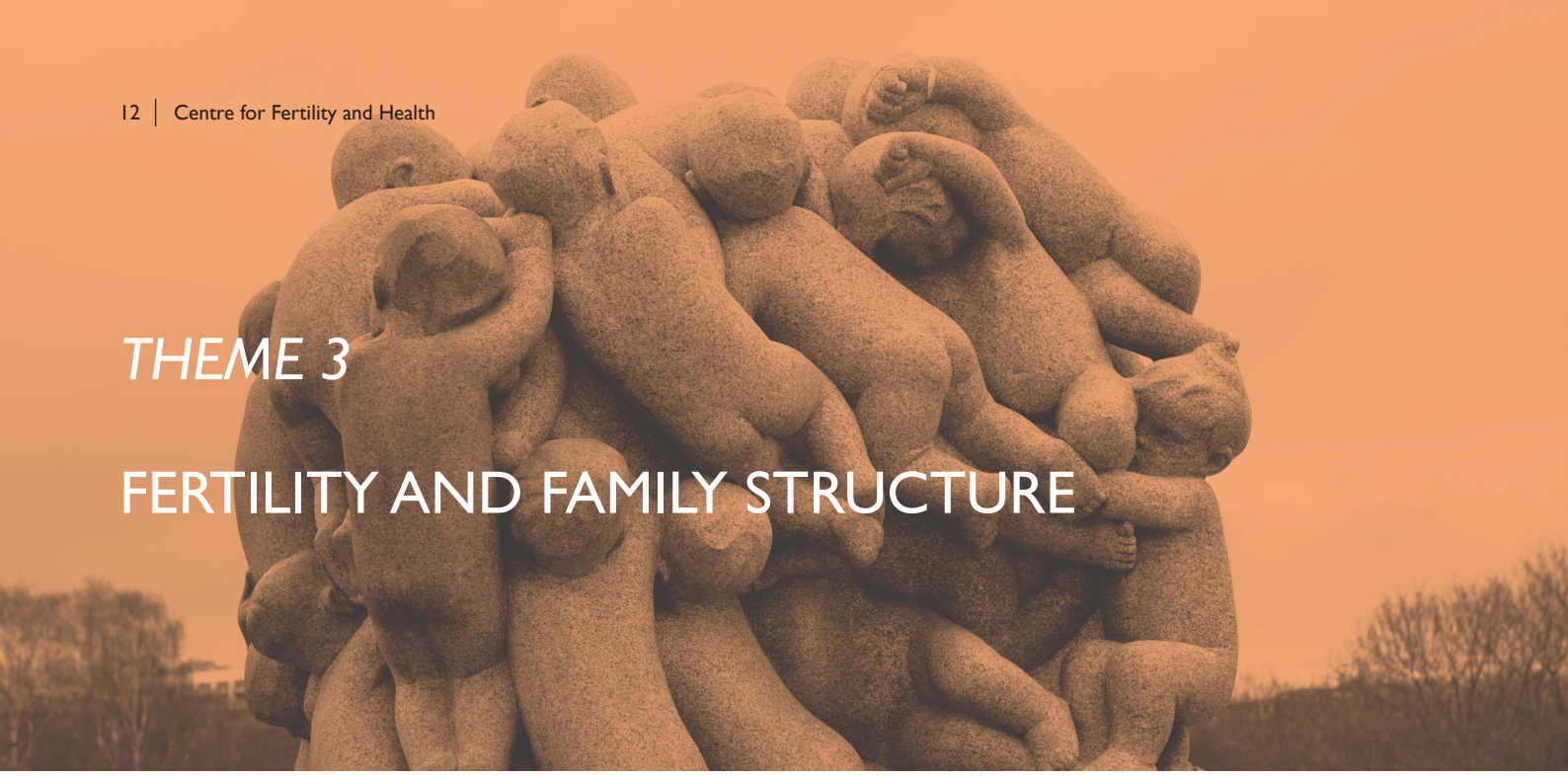


Figure 4. Wonders of nature.
Left: A human egg cell. ***Middle:*** A human embryo at the four cell stage, two days after in vitro fertilisation. ***Right:*** A human blastocyst, five days after in vitro fertilisation. The inner cell mass of the blastocyst subsequently forms the embryo, and the the other cells of the blastocyst forms the placenta and the fetal membranes.
Photo: Spiren Fertilitetsklinikk v/Thorir Hardarsson



THEME 3

FERTILITY AND FAMILY STRUCTURE

The demographic setting

As age at first birth has increased and the number of children born to each woman has decreased over the past decades, more people are ending up childless. Additionally, there have been marked changes in marriage, divorce and cohabitation patterns over the last half century: The age at marriage and the proportion of people who never marry have increased, while divorce rates have escalated. Couples living together in consensual unions have largely compensated for this shift away from marriage, but these unions are much more unstable. In combination with an increase in the proportion of children born outside of marriage, and most commonly to cohabiting parents, these patterns and trends in partnership instability have led to a sharp rise in the proportion or children who experience parental disruption. For example, 39% of 17-year old children in 2015 did not live with both their parents. Because many parents form new partnerships after disruption, and often have children in these partnerships, families are becoming more and more complex.

The changes in marriage, divorce, cohabitation and family structure have been influenced by (and contributed to) the fertility changes, and the two sets of changes have also been driven by many of the same forces. Because of this close relationship between fertility and family behaviour, it is reasonable to take both into account in studies of health implications.

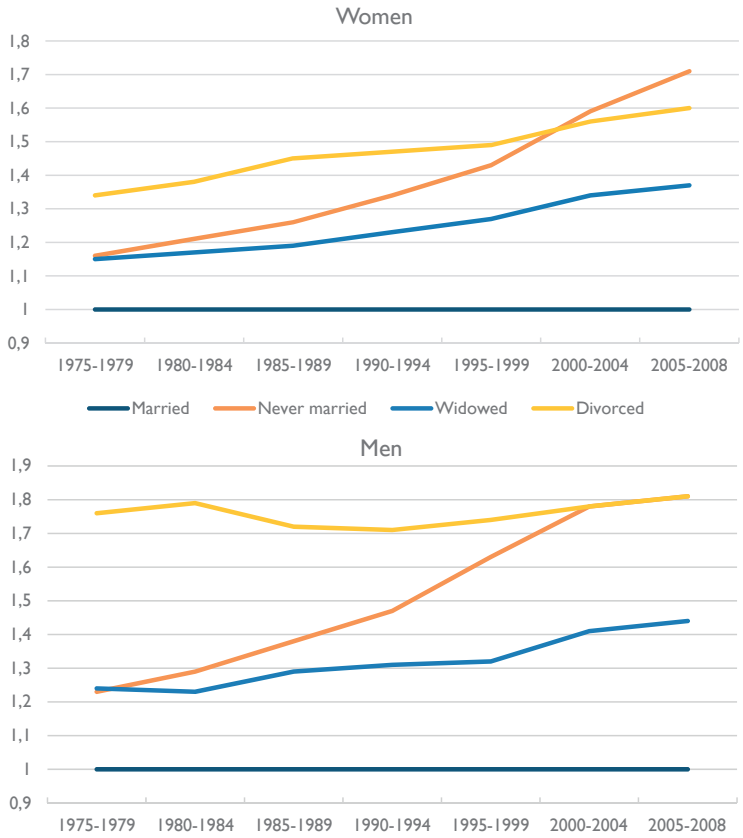


Figure 5. Mortality of non-married individuals relative to that of married individuals (odds ratio), by period, controlled for age differences. *Source: Kravdal et al. (2018)*

Goals

Our goal is to contribute to better understanding of how the number of children, age at first birth, length of birth intervals, and partnership disruptions affect the health of parents, and how the number of siblings, birth interval lengths and parental disruption affect offspring health. The reproductive factors may affect the parents' health through both biological mechanisms (linked to physiological processes during pregnancy or lactation) and social pathways. As examples of social pathways, the number of children likely affects a person's lifestyle and may be important for access to support in old age, whereas early entry into parenthood may disrupt education or work careers, with later implications for health. Comparisons between fertility-health associations among women and men shed light on the relative importance of biological and social mechanisms.

Number of children and adult health

In 2018, we analysed associations between number of children and adult health outcomes. Especially, we paid attention to cardiovascular mortality and the risk of being diagnosed with inflammatory bowel disease. The latter was done in collaboration with two gastroenterologists at the Oslo University Hospital, and a paper indicating a protective effect of pregnancy on the risk of developing Crohn's disease was submitted to a journal early in 2019.

Furthermore, a paper discussing the scientific and political value of research on effects of number of children on parents' health and other outcomes was finalized in 2018 and published in the *Journal of Population Research* early in 2019.

In these studies, the observation that those who have many children also tend to have been younger when they have become parents has been taken into account, which itself may affect later health.

The importance of the number of older siblings (birth order), maternal age, and birth interval for child mortality in sub-Saharan Africa

In 2017, we finished research on the effects of reproductive factors on child mortality in sub-Saharan Africa, and we published a paper in *Population Studies* in 2018. The study was based on data from Demographic and Health Surveys in 28 countries. The study confirmed that short birth intervals are strongly associated with high child mortality. We also observed an adverse effect of higher maternal age, while higher birth order was found to have a protective effect.

The paper discusses the implications of various alternative reproductive "strategies" from a novel perspective, taking into account three issues. One issue is that that there may be long-term consequences of the age at first birth, in the sense that a relatively low age at first birth tends to also lead to low age in subsequent births, which may affect the mortality of those children. Another relevant issue is that a short interval to the next birth does not only increase the chance that the next child dies; given the mother's age at the most recent previous birth, a short interval to the next child also means that she will be younger when that child is born, and likely also at subsequent births, which has additional impact. Thirdly, if a woman has a child at a younger age, the birth will necessarily take place in an earlier calendar period. The latter is likely to have importance as well, for example because of continued general improvements in nutrition, sanitation and health care.

Marital status and mortality

Our research has shown that the mortality gap between married and non-married individuals in Norway has become larger over recent decades, similar to what has been observed in some other rich countries. Among the never-married in Norway, mortality did not fall over the last decades of the 20th century, and in 2005-08, mortality was as high for this groups as for the married group three decades earlier. The divorced, who had the highest mortality in first part of the period, had lower mortality than the never-married in 2005-08. A paper with emphasis on the combined importance of marital status and education was published in *Population and Development Review* in 2017. In 2018, we published another paper (with Emily Grundy at the University of Essex) in *Demographic Research*. It included additional details about the increasing mortality disadvantage among the non-married. However, the main message of the paper was that education contributes very little to the increasing mortality differences between marital status groups. The conclusions from the two papers were disseminated broadly through a Policy Brief published by Population Europe.

Effects of parental disruption on child health

In 2018, we finalised an analysis of how children's age at parental divorce affects the children's use of antidepressants in early and mid-adulthood, and we published a paper (with Emily Grundy) in *Population Studies* early in 2019. The study showed that children who were older when the divorce occured were more likely to purchase anti-depressants at age 20-44. The relationship between age at parental divorce and depression was only evident among women and those whose mothers had low education. The relationship was partly a result of lower educational attainment among those who experienced the divorce at the lowest age. To conduct this study, we used data from registers, including the Prescription Database.

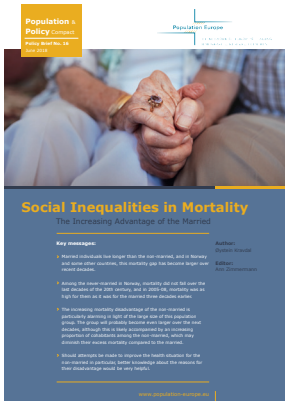


Figure 6. Facsimile of Population Europe Policy Brief No. 16, 2018.

The importance of interpregnancy intervals for pregnancy outcomes and child health.

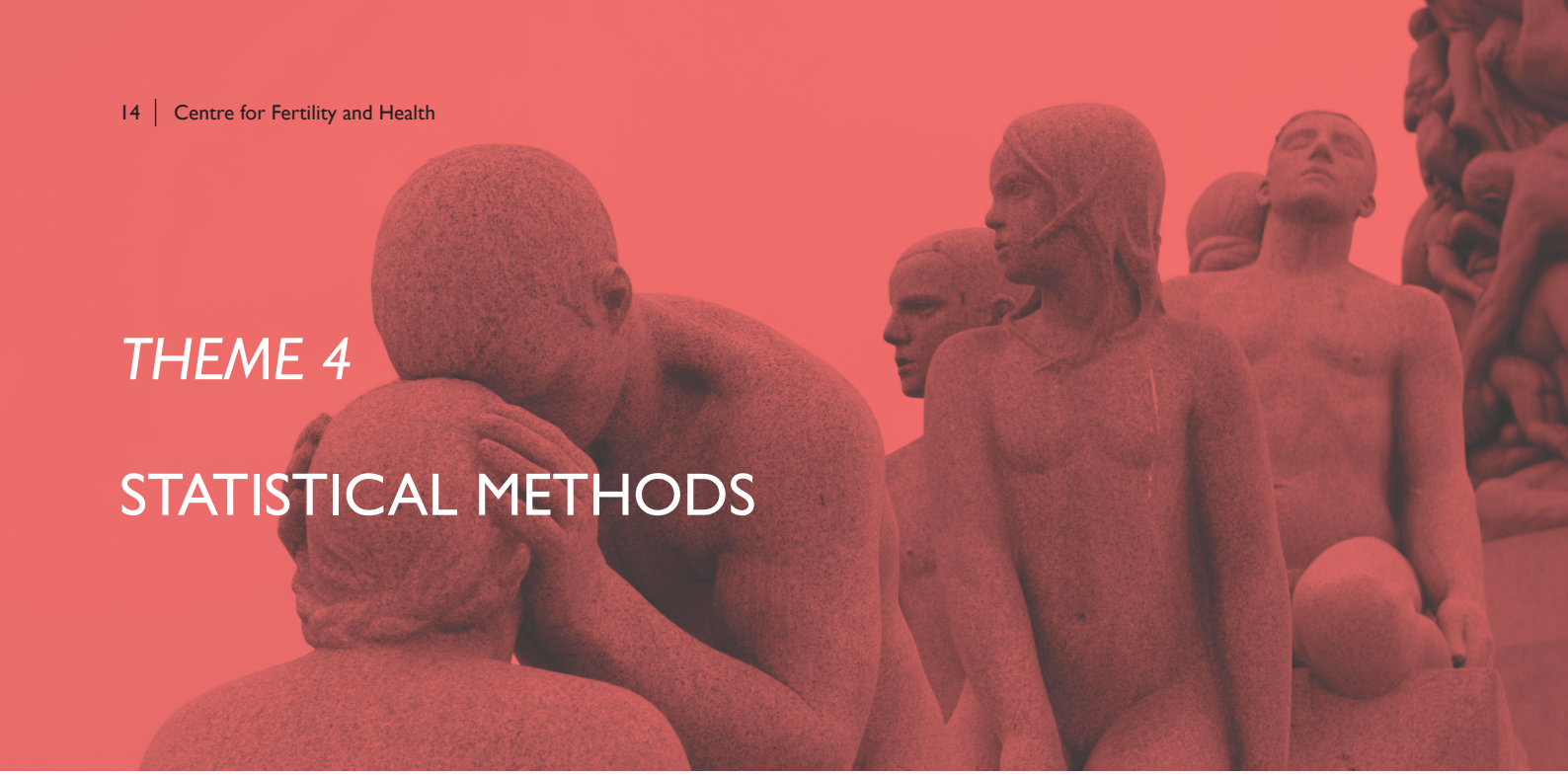
Birth intervals are often quite short also in rich countries. Research has shown that starting childbearing at high age – which is increasingly common – is associated with short successive pregnancy intervals. We work with Australian (Curtin University, Perth) and Finnish researchers (Institute of Health and Welfare, Helsinki) on combining registry data from several countries to study the effects of intervals between pregnancies. With a large combined study population, we are able to study rare outcomes such as intervals after stillbirths and other adverse pregnancy outcomes.

The gender gap in education

In 2018, we started a project aimed at understanding the health consequences of gender differences in educational attainment. These consequences involve fertility and family structure. For example, less educated men are less likely to form stable partnerships and have children, and if they do marry or cohabit, the partner also tends to have low education. In past years, low education has been associated with higher fertility for women, but this is about to change because of women's new roles in the family.

Future plans

From 2019 or 2020, our research will be based on a larger register data file. In 2018, we obtained ethical approval to construct a data set covering the whole Norwegian population and including information from a wide array of registers.



THEME 4

STATISTICAL METHODS

The Centre's interdisciplinary approach to understand health implications of the recent changes in fertility patterns and family structure requires close collaborations between different disciplines, as well as coordination and development of research methodology. While the different disciplines at the Centre have different traditions, different terminology and different approaches to research methodology, statistical modeling is a unifying theme across all disciplines. We have therefore added statistical methodology as a new, central theme to the original four themes of focus. Figure 7 illustrates some of the many interdisciplinary links in the use of statistical analyses.

Our research projects employ numerous statistical analysis strategies where we contribute actively to the methods development. We describe some key methods below.

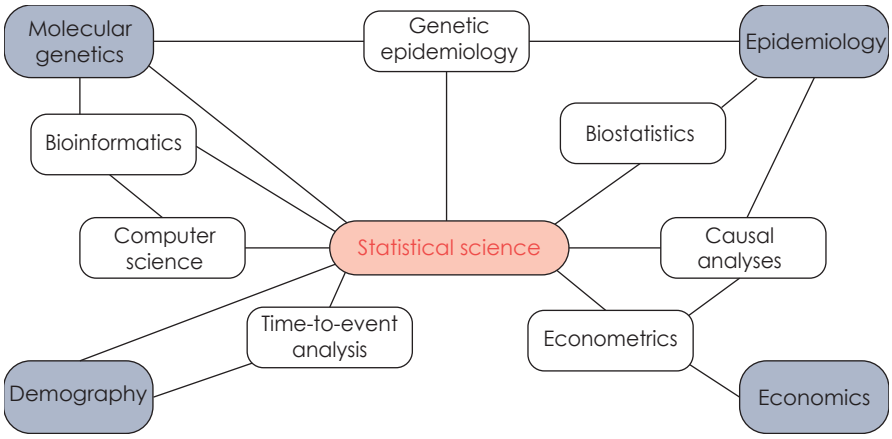


Figure 7. Statistical methodology at the Centre.

Haplin and genetic association analyses

Most of our research on genetic factors in relation to fertility, pregnancy outcomes, and health consequences of ART procedures is focused around nuclear families, in particular with basis in the MoBa study. Haplin is an open source statistical package developed in the R programming language, a free software environment for statistical computing and graphics. Haplin was initially published by Håkon Gjessing et al. in 2006, and is being developed continuously to adapt to new research challenges at the Centre. We use Haplin in analyses of triad data (nuclear families), where it is applied to GWAS data. Haplin is designed to discover a variety of genetic effects within a family triad, such as parent-of-origin effects, effects of fetal and maternal genes, X-chromosome genes with or without X-inactivation, gene-environment interactions etc. Recent implementations allow for the inclusion of methylation (EWAS) data, which are central to our fertility analyses. Haplin is available for multicore computations at the TSD platform at the University of Oslo. Figure 8 illustrates a typical combination of case-parents triads and control-parent dyads available for analysis.

Time-to-event analyses

Nearly all statistical analyses at our Centre involve time scales. A typical time scale in demography is age of an individual, used when analysing age at first birth, age at death etc. Similarly, time from first to second birth is used to study factors that determine birth spacing and the total number of children to a mother. In perinatal epidemiology, gestational age is a useful time scale for studying exposures throughout pregnancy, including the potential effects of ART procedures. A thorough understanding of how to analyse data on a time scale is essential to avoid selection biases due to truncated time spans,

frailty phenomena, and other challenges in time-to-event analyses. Our group has extensive experience in research on time-to-event analyses, and are continuously developing new strategies to integrate genetic data with time-to-event data, accounting for familial correlations, etc.

Causal analyses and Mendelian randomisation

Understanding whether a medical procedure such as ART, an individual's life style choices, family planning etc. have causal effects on health outcomes is central to our research. While a well-designed randomised clinical trial is the gold-standard for determining causal effects, they are impossible to conduct in most epidemiologic, economic, and demographic research. In econometrics, statistical methods and statistical designs to determine causality from observational data have been developed and extended for decades. More recently, such methods have been transferred to and further developed in epidemiologic and demographic research. As an example, instrumental variable models have found increasing use in genetic epidemiology, where genes are used as an "instrument" to reveal causal relationships between exposures and outcomes, and eliminate confounding effects of unmeasured variables. Known as Mendelian randomisation, this methodology has been implemented using, for instance, polygenic risk scores.

Mendelian randomisation has been a central topic of research at the University of Bristol, UK. In 2018, we strengthened our ongoing collaborations with several researchers from the University of Bristol. Two young researchers were awarded our Gro Harlem Brundtland Visiting Scholarship, and have spent time at the Centre in 2018 and 2019.

Another strategy to focus the understanding of causal mechanisms is the fixed effect analysis. A statistical model frequently used in demographic research, fixed effect analysis has recently found more extensive use in epidemiology as a way of accounting for maternal genes and other factors that remain constant from pregnancy to pregnancy.

The challenge of imperfect data

Data are in practice imperfect in several ways. One pervasive problem is *missing data* where some observations are not recorded. Another problem is *measurement error* where only fallible measures are available for variables of interest. In both cases, invalid statistical inference is likely to result if the problems are not appropriately addressed. Moreover, data often contains units nested in clusters. For instance, in *longitudinal data* repeated measurements on health status can be nested in persons and in *multilevel data* observations on persons can be nested in institutions such as hospitals. In both cases, the nested structure is likely to induce dependency among the units in the datasets and invalid statistical inference will result if such dependence is ignored. At the Centre, we are actively working on developing novel methods for handling imperfect data.

Examples of textbooks in statistical methods written by researchers at the Centre.

High-dimensional data, prediction, and variable selection

Based on the results from extensive GWAS and EWAS analyses, there is a need to develop prediction methods and scores by selecting subsets of SNPs or CpGs that are of manageable size but retain sufficient predictive power. Such scores are becoming increasingly popular in genetic research to construct, for instance, polygenic risk scores for fertility, propensity scores for ART procedures, prediction models for epigenetic age acceleration, etc. The necessary statistical methodology is bordering to bioinformatics, statistical learning, and machine learning. Our group has published new scores for "epigenetic gestational age" that are already being applied in international research projects.

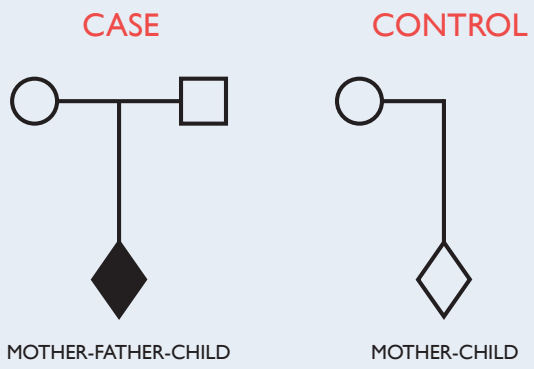
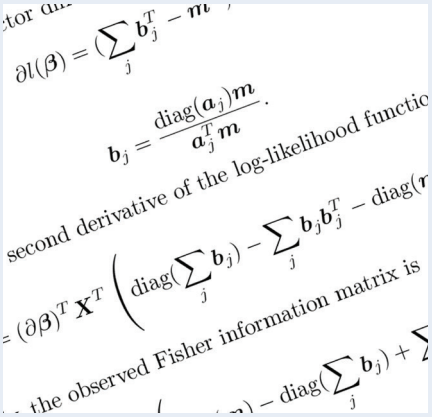


Figure 8. Illustration of a typical combination of case-parents triads and control-parent dyad available for analysis.



Power and sample size calculations with Haplin. *Article in press, Gjerdevik et al. 2019*

THEME 5

INTERGENERATIONAL TRANSMISSION OF HEALTH

Health factors can be transmitted to subsequent generations in several ways. First, certain characteristics of the parents that are important for their own health, such as their socioeconomic resources, lifestyles and attitudes may be passed on to their children through various types of "social transmission". Second, a trait from the parents can be inherited through genes. Third, the parents' health may affect the daily life in the home, their ability to care for the children, and the children's education and income, all of which in turn may be important for the children's health.

Relative importance of genes and environmental factors

We will estimate the relative importance of genes and environmental factors in transmission of certain diseases and indicators of wellbeing. We will use GWAS data from the Norwegian Mother and Child Cohort Study to calculate genetic risk scores for both adults and offspring. Thus, we can examine the interaction between genetic and social factors with respect to the risk of specific diseases.

In 2018, we published a paper in *Hypertension* investigating maternal and paternal height and the risk of preeclampsia. Tall women have been found to have a lower incidence of preeclampsia. This points to a possible biological causal effect, but may also be because of socioeconomic confounding. Our analysis showed that the association between maternal height and preeclampsia is unlikely to be due to confounding by familial, socioeconomic factors or by fetal genes related to height.

Transmissions of disease and risk factors

Using data from two large cohort studies, Cohort of Norway (CONOR) and the Norwegian Mother and Child Cohort Study, we will analyse transmissions of disease and risk factors (such as smoking, high caloric intake diets, and low levels of physical activity) across three generations, from grandparents via parents to children. Detailed questionnaire data, physiological measures and physical tests will allow us to consider a broad range of biological and socio-economic factors that can be involved.

Analyses across multiple generations

We further plan to extend these perspectives to more than three generations by using historic demographic data that include seven to nine generations. We will assess whether the health of children today is related to the health of their ancestors. We will take into account the longevity of past generations, and also explore influences via family size and structures, socioeconomic resources and environmental contexts. For these studies, we will make use of the National Historical Population Register.

In 2018, we published a paper in *Nature* emphasising that lifestyle during adolescence does not only have an impact on youth's own health, but also on the health of future generations. Thus, facilitating good health choices in early life should be a priority in public health programs.

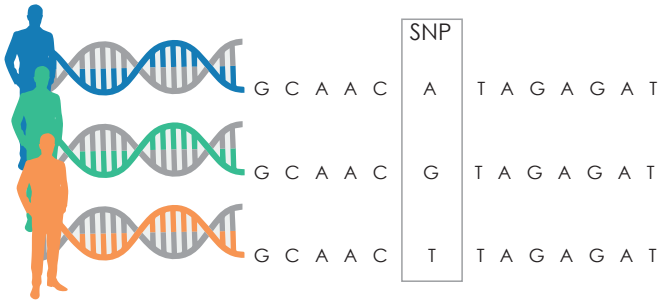


Figure 9. Genome-wide association studies (GWAS) are analyses of genetic variants observed in different individuals to understand their association with phenotypical traits. The genetic variation observed in the genome is often a variation in a single base pair in the DNA, called single-nucleotide polymorphisms, or SNPs. One can compare such variations with mutations, but whereas a mutation is quite rare (in less than 1% of the population), SNPs are more common. GWAS are useful analyses to know which genetic variations are associated with a phenotype, but they cannot be used to determine causality, e.g. that one genetic variation leads to a certain disease.

KEY PROJECTS

Reproduction, partner disruption and health

The main aim of the project is to understand the health consequences of changes in fertility patterns and partner disruption. The health consequences are studied at the population level, with special focus on mortality and morbidity from cancer, cardiovascular diseases and mental disorders.

The data collected for this project constitutes the basis for many of our coming research papers. Our research questions are divided in four sub-projects:

- How do maternal/paternal age at birth, number of siblings, and age interval between siblings affect children's health?
- How do the number of children (including childlessness), age at first birth, and interval between births affect adult health?
- How does disruption of parental relationships, and possible parental re-partnering, affect children's health?
- How does disruption of relationships, and possible re-partnering, affect the health of the involved adults?

In 2018, the project was approved by the Regional committees for medical and health research ethics, and we started the work to apply for access to data from various registers.

Key personnel at the Centre: Per Magnus, Øystein Kravdal, Kåre Bævre, and many more from the Centre staff.

START - Study of assisted reproductive technology - epigenetic mechanisms

The main aim of the project is to understand health consequences of subfertility in women and men, and to examine how genetic influences and epigenetic differences are associated with subfertility and the use of assisted reproductive technologies (ART). Both genetic and epigenetic mechanisms play a role in health outcomes after the use of ART.

In 2018, we started pulling 6048 samples from the biobank of the Norwegian Mother and Child Cohort Study. The samples include 1000 trios of mother/father/children born after ART and 1000 control trios. These samples will be analyzed with the new methylation EPIC array covering more than 850 000 methylation sites across the genome.

The project is funded by the Research Council of Norway through the Centre of Excellence grant.

Key personnel at the Centre: Siri E. Håberg, Robert Lyle, Håkon Gjessing, Rolv Terje Lie, Jon Bohlin, Astanand Jugessur, Christian Page, Julia Romanowska, Maria C. Magnus.

ART - Assisted Conceptions - Pregnancy and childhood outcomes

In this project we combine Norwegian registry data and questionnaire data from the MoBa cohort study to investigate causes and consequences of subfertility and assisted conceptions. The project was initiated in 2014 and has been updated with new datasets in 2018. Main outcomes include fetal growth, gestational length, fetal loss, vanishing twins, and health in children and parents with subfertility and use of ART.

The project is funded by the Research Council of Norway through the Centre of Excellence grant.

Key personnel at the Centre: Siri E. Håberg, Allen Wilcox, Maria C. Magnus, Rolv Skjærven, Nils-Halvdan Morken, Håkon Gjessing, Laura Oakley, Liv Bente Romundstad.

National Historical Population Register for Norway (HPR) 1800-2024

The main aim of the project is to build a longitudinal population register including all persons who lived in Norway in the period 1800-1964, and which will be integrated with the National Population Register. This register will be very valuable in studies of the population over the life course, and for the research in the Centre. The Historical Population Register is constructed from linking data from censuses, church books and other primary sources.

In 2018, researchers at the Centre were partners in a new application to the Research Council of Norway aiming at continuing and extending the present project. The main aims in this new project is to complete the construction of HPR, but also to integrate it into open data infrastructure where the different users of additional thematic historical registers can cooperate and add new data to the benefit of all users, where HPR will facilitate full linkage of these historical registers and datasets with existing modern microdata.

The START team at a project meeting in March 2019. ***From left to right:*** *Julia Romanowska, Ellen Carlsen, Håkon Gjessing, Maria Magnus, Siri E. Håberg, Gemma Sharp, Jon Bohlin, William Denault, Kristine Løkås Jacobsen, Astanand Jugessur, Per Magnus, Haakon E. Nustad, Christian Page.* ***Sitting in front:*** *Rolv Terje Lie and Øystein Ariansen Haaland.* ***Not present:*** *Miriam Gjerdevik and Robert Lyle. Photo: Fredrik Swift*

The project is funded by the Research Council of Norway's FORINFRA program since 2013.

Key personnel at the Centre: Kåre Bævre and Per Magnus.

HEALTH-GAP. Health, maturity, and the gender gap in education

The primary objectives of the project are to understand the health consequences of gender differences in educational attainment and school performance and to examine whether the difference in timing of physical maturity between girls and boys is a major explanation for the observed gender gaps in education.

In 2018, two researchers were hired at the Centre to work on this project, and we have established collaborations with Institute for Social Research, Norway and the University of Bristol, UK. The topic received much attention in 2018, particularly in connection with the work by a committee (led by Camilla Stoltenberg) which was appointed by the government in 2017 to gather knowledge about the gender differences in school, and suggest measures to counteract adverse gender differences in educational attainment and school performance. Educational attainment is likely to affect fertility and health in several ways. Firstly, more educated men and women have increased their fertility compared with their less educated peers. Secondly, combining health risks of low educational attainment with little social support in terms of family network may be particularly damaging for health, and perhaps especially for men's health. Thirdly, an assortative mating among people with low education may further exacerbate individual health risks in this group.

The project is funded by the Research Council of Norway's BEDREHELSE program.

Key personnel at the Centre: Fartein Ask Torvik and Martin Flatø.

The Burden of Obesity in Norway

The main aim of the project is to study the impact of obesity on morbidity, mortality, health service use and social insurance benefits in Norway. The project aims to gain a deeper understanding of the total burden of obesity in Norway by estimating individual trajectories and cost of illness by different demographic and social characteristics. Secondly, we aim to elucidate the causal impact of obesity on health and health service use by the use of genetic markers as natural experiments.

In 2018, the project team published one paper in *BMJ* on the impact of obesity on mortality and another paper on the impact of obesity on health service use is currently under review. Further investigations into the causal effect of obesity on fertility/birth outcomes/relationship status is being pursued.

The project is funded by the Research Council of Norway's FRIMEDBIO program (Young Research Talents).

Key personnel at the Centre: Jonas Minet Kinge, Christina Edwards.

Evaluation of free school fruit on childhood growth and obesity: a natural experiment

The primary objective of the project is to estimate the effect of the free school fruit program on childhood growth and obesity.

In the period 2007 to 2014, pupils in junior high-schools and combined primary and junior high-schools were given a free fruit/vegetable each day, while pupils in primary schools were not. We have measured height and weight among 13-year olds in more than 150 schools to evaluate the effects of this natural experiment. The data are now ready for analysis.

The project is funded by the Research Council of Norway's BEDREHELSE program.

Key personnel at the Centre: Per Magnus.

InPreSS - International Pregnancy Drug Safety Studies. Short and long-term safety of drug use in pregnancy

InPreSS is an international collaboration to study the safety of drug use in pregnancy. The overarching objective is to better understand the consequences of in-utero drug exposure on fetal development, birth defects and longer-term outcomes (neurodevelopment outcomes and academic performance) in the child, comparative drug safety, as well as maternal social and health consequences of discontinued drug treatment.

The project was started on June 1, 2018 and is a collaboration between partners from the five Nordic countries, Australia and USA.

The project is funded by the Research Council of Norway through the BEDREHELSE program.

Key personnel at the Centre: Kari Furu, Maria C. Magnus and Siri E. Håberg.

Telomere length, epigenetic age and T cells in women who give birth at an older age

This project aims to investigate female fecundity in the context of three major indices of biological age: telomere length, epigenetic age, and immune status. The hypothesis is that women with a longer telomere length, younger epigenetic age and healthier immune status than their peers have an increased ability to give birth to their first child at

an older age.
DNA samples of 2000 trios (mother, father and newborn) from the Norwegian Mother and Child Cohort Study (MoBa) were selected for this project. Rutgers University (USA) will measure leukocyte telomere length in these 2000 trios, whereas UCLA, United States will measure DNA methylation in 1000 of the mothers aged 32 years and above.

In 2018, DNA from 500 trios was sent to Rutgers University for analysis. A PhD student in the project, Yunsung Lee, received a mobility grant from the Norwegian Research Council to travel to UCLA in the US. He has been visiting Prof. Steve Horvath's lab at UCLA from November 2018 to April 2019 to pursue epigenome-wide association analysis (EWAS) of telomere length using data from the Women's Health Initiative, the Framingham Heart Study, and the Jackson Heart Study.

The project is funded by the Research Council of Norway's FRIPRO program.

Key personnel at the Centre: Astanand Jugessur, Per Magnus, Håkon Gjessing and Jennifer Harris. PhD candidates: Kristine Løkås Jacobsen and Yunsung Lee.

Telomeres and female fecundity

The background of the project is the observation that women with delayed menopause and those who give birth to children later in life show less cardiovascular disease and live longer than other women. Women with constitutively long telomere length have delayed menopause, show less cardiovascular disease and also live longer than other women.

The central hypothesis of this proposal is that women who bear children later in life without the use of ART might have a constitutively long telomere length. The aims of the study are: 1) to measure telomere length in 1700 mothers who gave birth at ages 18 years or older, including 1000 mothers who gave birth at the age 35 years and older; 2) measure telomere length in 300 mothers who gave birth at the age of 35 years and older with the aid of in-vitro fertilization; 3) measure telomere length in the 2000 fathers (the sexual partners) of the mothers in aims 1 and 2); and 4) to measure telomere length in newborns of these parents.

The project is funded by the US National Institutes of Health (NIH).

Key personnel at the Centre: Astanand Jugessur, Per Magnus, Håkon Gjessing. PhD candidates: Kristine Løkås Jacobsen, William Denault and Yunsung Lee.

The intrauterine redox state and telomere length in the newborn

The aim of the project is to examine (1) the association between newborn's leukocyte telomere length and mitochondrial genotypes, and (2) associations between newborn's leukocyte telomere length and maternal smoking during pregnancy.

The projects was granted funding from the Research Council of Norway's FRIMEDBIO program in 2018.

Key personnel at the Centre: Håkon Gjessing, Astanand Jugessur and Jennifer R. Harris.

Dimjob - Social, demographic and health dimensions of technology-induced job loss

The project will study Norwegian population registries and surveys on occupation and firm data, education, cognitive test performance, personality, coping, health, intergenerational data, social isolation, physiological and mental health trajectories. We will study how these factors relate to how individuals respond in terms of demographic, social and health outcomes, including quality of life, re-employment, disease incidence, training and demographic outcomes (e.g., partnership stability, childbearing, internal migration).

The projects was granted funding from the Research Council of Norway's VAM program in 2018.

Key personnel at the Centre: Vegard Skirbekk.

Metabolic profile and IVF, pregnancy, perinatal and longer-term outcomes

We will combine metabolic profiles, genome-wide genotypic data, and clinical factors to understand causal mechanisms for, and accurately predict, adverse pregnancy, perinatal and postnatal outcomes in in vitro fertilisation (IVF) and spontaneously conceived pregnancies. Differences in pregnancy metabolic profiles are likely to be important, but it is only recently that studies of pregnant women have detailed measurements of metabolic profiles assessed during pregnancy.

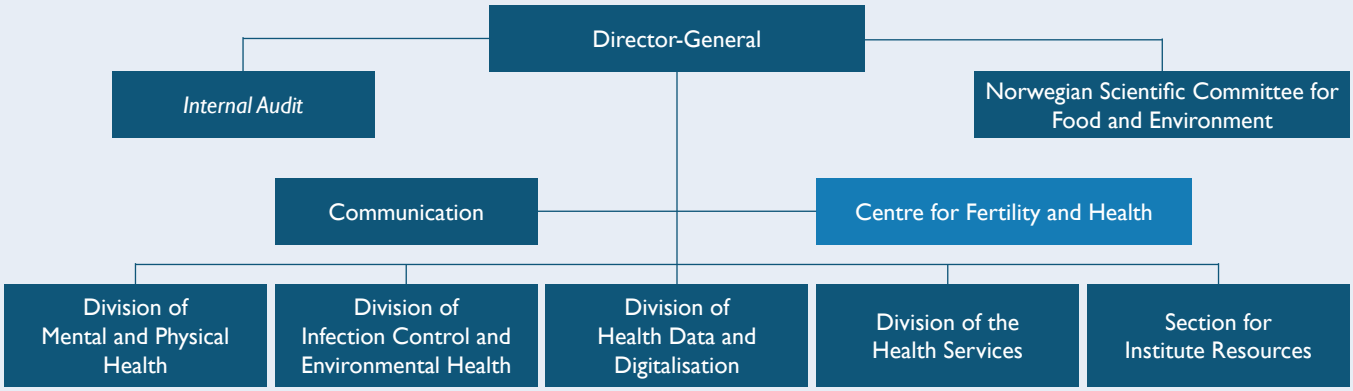
We plan to add metabolomic profiles to pregnancy samples on a subgroup of 16 000 women and 5000 of their male partners in MoBa who have genome-wide genotypic data on trios. These data will contribute to evidence that will enhance our understanding of the role of pregnancy metabolism on pregnancy and perinatal outcomes. We will use machine learning methods to develop prediction algorithms for each adverse outcome, and also for 'healthy' pregnancy, and test the discrimination and calibration of these, as well as compare them to similar metrics for prediction using established risk factors collected at the first antenatal clinic.

The project is funded by grants to professor Deborah A Lawlor (ERC Advanced Grant and UK National Institute of Health Research Senior Investigator award).

Key personnel at the Centre: Siri Eldevik Håberg, Per Magnus, Maria C. Magnus.

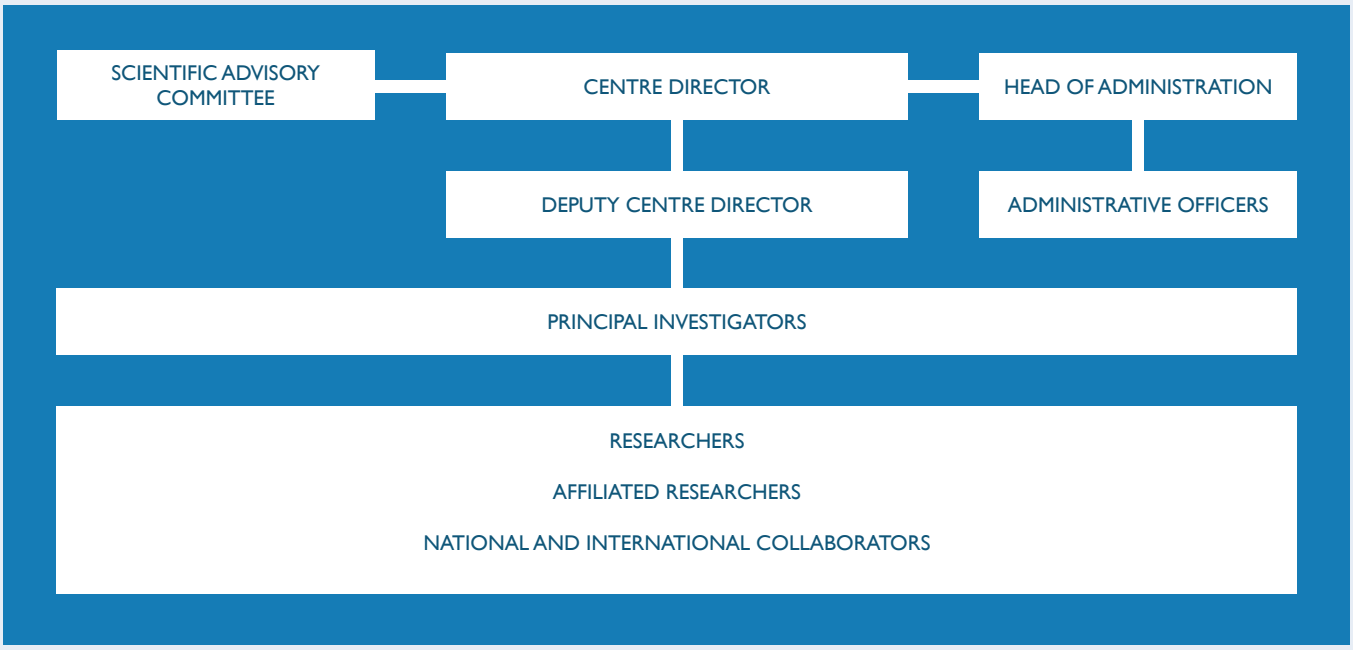
ORGANISATION

ORGANISATION CHART FOR THE NORWEGIAN INSTITUTE OF PUBLIC HEALTH



ORGANISATION OF THE CENTRE

CENTRE BOARD	CORE GROUP	CENTRE TEAM
Top Management Group at the Norwegian Institute of Public Health	Centre Director Deputy Centre Director Principal Investigators Head of Administration	Core Group Researchers and Staff Affiliated Researchers



CORE GROUP

Centre Director Per Magnus

Per Magnus is a physician with a background in medical genetics. He has been employed as an epidemiologist at the Norwegian Institute of Public Health since 1985, and is also adjunct professor at the Institute of Health and Society at the University of Oslo. He has worked on a series of public health challenges, such as infections (HIV, pandemic influenza), childhood asthma, autism, and chronic fatigue syndrome, although his main interests have always been genetic and perinatal epidemiology. He has been active in building networks between epidemiologists in Norway and was the first Head of the Norwegian Epidemiological Association. He has written textbooks on epidemiology and project planning, and teaches genetic, epidemiological and social medicine research. He has initiated a series of cohorts and case-control studies. He had a key role in establishing the Norwegian Mother and Child Cohort Study (MoBa), and has been its principal investigator for the past twenty years.

Deputy Centre Director Siri E. Håberg

Siri Eldevik Håberg is a physician with main research interest in perinatal epidemiology. She is well experienced in combining data from cohort studies, biological analyses and national registries. Håberg's current research focuses on the causes of fertility problems and fetal loss, and risk factors and consequences of assisted reproductive technologies. Her work has involved registry based population studies, and studies of genetic and epigenetic associations with pregnancy exposures, pregnancy outcomes and early life diseases. Håberg has also been involved in a number of registry-based projects studying influenza, safety of vaccinations and antiviral medications in pregnancy, childhood and in the general population. This research has focused on the link between immunology and neurological, neurodevelopmental and autoimmune diseases. Håberg leads and collaborates with several international research groups on environmental exposures, pregnancy and child health outcomes.

Principal Investigator Vegard Skirbekk

Vegard Skirbekk is a population economist and social scientist specialising in demographic analysis and cohort studies. He holds a professorial position at the Population and Family Health at Colombia Aging Centre at Columbia University, USA. Skirbekk received his PhD from Rostock University, Germany and has also worked at the Max Planck Institute for Demographic Research. He has two decades of international experience and has held professorships and scientific leadership positions in Austria and Germany. He has received research grants from ERC, PEW and UNESCO. Skirbekk's main research focus is on health, productivity, and associated determinants from a multidisciplinary perspective, with an emphasis on the role of changing labor market demands, technological and cultural changes as well as variation in the attitudes, beliefs, and competences of new cohorts. He has published widely on comparative health and cultural studies for countries from all world regions. Skirbekk has worked extensively on causality, global comparative assessments and projections.

Principal Investigator Øystein Kravdal

Øystein Kravdal is professor of demography at the Department of Economics, University of Oslo, since 1994. Since 2009 he has also worked at the Norwegian Institute of Public Health. His main research interest is how socio-economic resources influence and are influenced by fertility and family behaviour, and how all these factors are associated with health and mortality. Most of his work has been based on register or survey data from Norway, but he has also done research on fertility and child mortality in India and sub-Saharan Africa. His papers have been published in demography, sociology, epidemiology and cancer journals. Kravdal was co-editor of *Population Studies* from 2004 to 2013, and has been a member of the Editorial Board of the *European Journal of Population* since 2001. He was member of the Council of the International union for the Scientific Study of Population from 2014 to 2017.

Principal Investigator Håkon Gjessing

Håkon Gjessing is a statistician with extensive experience in developing (bio) statistical and mathematical models. He is adjunct professor at the University of Bergen. One of his main research areas is statistical genetics, including classical biometrical modelling, as well as molecular genetics, including GWAS and methylation analyses. He has co-authored a book on statistical models in Event History Analysis, and has contributed extensively to perinatal epidemiology, including the development of the Norwegian national reference curves for ultrasound pregnancy dating and fetal size evaluation, as well as national reference curves for fundal height measurements. Gjessing has also developed the R-package "Haplin" for analysing genetic family triad data. He has (co) authored more than 120 scientific papers, and is currently Editor-in-Chief of the *Scandinavian Journal of Statistics*.

Head of Administration Fredrik Swift

Fredrik Swift holds a PhD in cardiac physiology from the University of Oslo, and has worked on cellular regulation of cardiac contractility during two postdoc positions in Norway and in Switzerland. He has long administrative experience and worked since 2013 as the Executive Assistant to the Director-General of the Norwegian Institute of Public Health, Camilla Stoltenberg, before becoming Head of Administration at the Centre for Fertility of Health in 2017.

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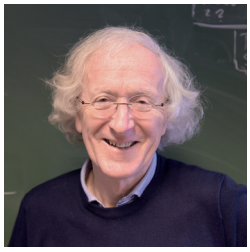

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George Davey Smith, *University of Bristol*
Andrew Wills, *University of Bristol*

NEW TEAM MEMBERS 2018

FOUR RESEARCHERS WERE RECRUITED IN 2018

Jonas Minet Kinge

Jonas Minet Kinge became a member of the Centre team in March 2018. He holds a PhD in Health Economics from University College London, and is also Associate Professor in Health Economics at the University of Oslo. His research interests include economics of obesity, social inequalitites in health, health services research, health expenditures and causal inference. Kinge is also a researcher in the Centre for Disease Burden at the Norwegian Institute of Public Health.

Maria C. Magnus

Maria C. Magnus became a member of the Centre team in August 2018. She holds a PhD in epidemiology from the University of Oslo, and her dissertation focused on prenatal and early childhood risk factors for asthma. After finishing her PhD in 2015, her research has mainly focused on female reproductive health and the risk of cardiovascular disease. She is currently involved in research looking at risk factors for miscarriage, consequences of use of assisted reproductive technologies on offspring health, and the risk of chronic diseases among infertile couples.

Fartein Ask Torvik

Fartein Ask Torvik became part of the Centre team in September 2018. His research interests include psychiatric epidemiology and the longitudinal development of mental disorders among adolescents and adults. He has been studying this in relation to normative and maladaptive personality traits, as well as substance use. He combines family designs, extended twin designs, genetic designs and registry data to address these topics. He currently work with gender differences school performance, aiming to understand how they arise and how they influence mental health.

Martin Flatø

Martin Flatø joined the Centre team in September 2018. He holds a PhD in demography from University of Oslo, and his dissertation focused on how gender dimensions in mortality and other outcomes in Sub-Saharan Africa are affected by changes in climatic conditions and parental preferences. He has since worked on the interplay between education and health and is currently involved in the Health-GAP project on causes and health consequences of gender differences in school performance.

THE GRO HARLEM BRUNDTLAND VISITING SCHOLARSHIP

The Centre is strongly committed to the education and engagement of young researchers and has established the Gro Harlem Brundtland Visiting Scholarship. This visiting scholar program hosts young researchers from Norway and abroad to engage in collaborative research and to participate in and enrich the research community at the Centre and at the Norwegian Institute of Public Health. The scholarship was announced for the first time in May 2018, and we plan to open for new applications on a yearly basis.

Robyn Wootton

Robyn Wooton was awarded the Gro Harlem Brundtland Visiting Scholarship in 2018 and stayed at the Centre from November 2018 until the end of February 2019.

Robyn graduated from the University of Warwick, UK in 2014 with a BSc (with First Class Honours) in Psychology. During her PhD at the University of Bristol, UK, she investigated the genetic aetiology of subjective wellbeing and other positive mental health outcomes including optimism, gratitude and trust. Her main research interest is genetic epidemiology of behavioral traits. During her stay at the Centre, Robyn has studied the effect of different health behaviours on fertility outcomes in the Norwegian Mother and Child Cohort Study using a method called Mendelian randomisation. The method uses genetic variants as instruments to account for reverse causation and confounding which often are sources of bias in epidemiological studies.

Gemma Sharp

Gemma Sharp was awarded the Gro Harlem Brundtland Visiting Scholarship in 2018, and stayed at the Centre for a short period in September 2018, then for a longer stay in March-May 2019.

Gemma holds a PhD in Reproductive Biology from the University of Edinburgh, UK, and is a Lecturer in Molecular Epidemiology at the University of Bristol, UK. Her main research interests relate to the prenatal origins of health and disease: how our genetics and the exposures we experience before birth might influence our lifelong health.

During her stay at the Centre, Gemma is writing a grant project proposal around developing epigenetic predictors of adverse pregnancy outcomes. She plans to combine the newly generated maternal DNA methylation data from the START project (MoBa) with data from two British birth cohorts: the Avon Longitudinal Study of Parents and Children (ALSPAC) and Born in Bradford (BIB). She is also conducting a research project looking at demographic, family and health factors associated with intended age at first birth in Understanding Society, a national survey of households in the UK.

SCIENTIFIC ADVISORY COMMITTEE

The Scientific Advisory Committee consists of leading scientists with expertise in epidemiology, demography, genetics and biostatistics. The Scientific Advisory Committee participate in discussions about the Centre's scientific strategy and give advice about scientific challenges and opportunities.

Members of the Scientific Advisory Committee at the opening symposium of the Centre organised in May 2018. *From left to right:* Roberta B. Ness, David Leon, Yudi Pawitan, Torkild Hovde Lyngstad, Dag Undlien. *Not present:* Matthijs Kalmijn and Susan Sawyer.

David Leon
Professor of epidemiology
Faculty of Epidemiology and Population Health
London School of Hygiene & Tropical Medicine, London, UK.

Roberta B. Ness
Rockwell professor of public health
University of Texas, Houston, USA.

Torkild Hovde Lyngstad
Professor of sociology
Department of Sociology and Human Geography
University of Oslo, Norway.

Susan Sawyer
Professor of adolescent health
The University of Melbourne
and
Director of the RCH Centre for Adolescent Health, Australia.

Yudi Pawitan
Professor of biostatistics
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Sweden.

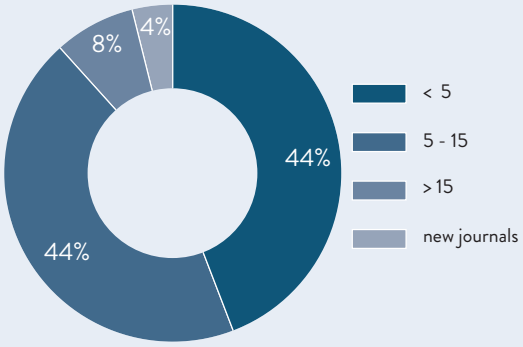
Dag Erik Undlien
Professor of medical genetics
Department of Genetics
Oslo University Hospital
University of Oslo, Norway.

Matthijs Kalmijn
Professor of sociology and demography
University of Amsterdam, Netherlands
and
Senior Researcher at Netherlands Interdisciplinary Demographic Institute.

The mandate of the Scientific Advisory Committees is to:

- Take part in discussions of the Centre's research strategy and scientific challenges throughout the entire project period. The committee may also provide advice on other types of issues.
- Provide strategic advice to the Centre, based on international trends and scientific development within the field of fertility and health. As far as possible, the SAC should also be able to provide advice that is directly relevant to Norwegian needs and strategies.
- Assume an active role in monitoring the performance and scientific excellence of the Centre.
- Provide annually a short status report on the development of the Centre, drawing on annual reports and other material made available by the Centre.

KEY INDICATORS 2018



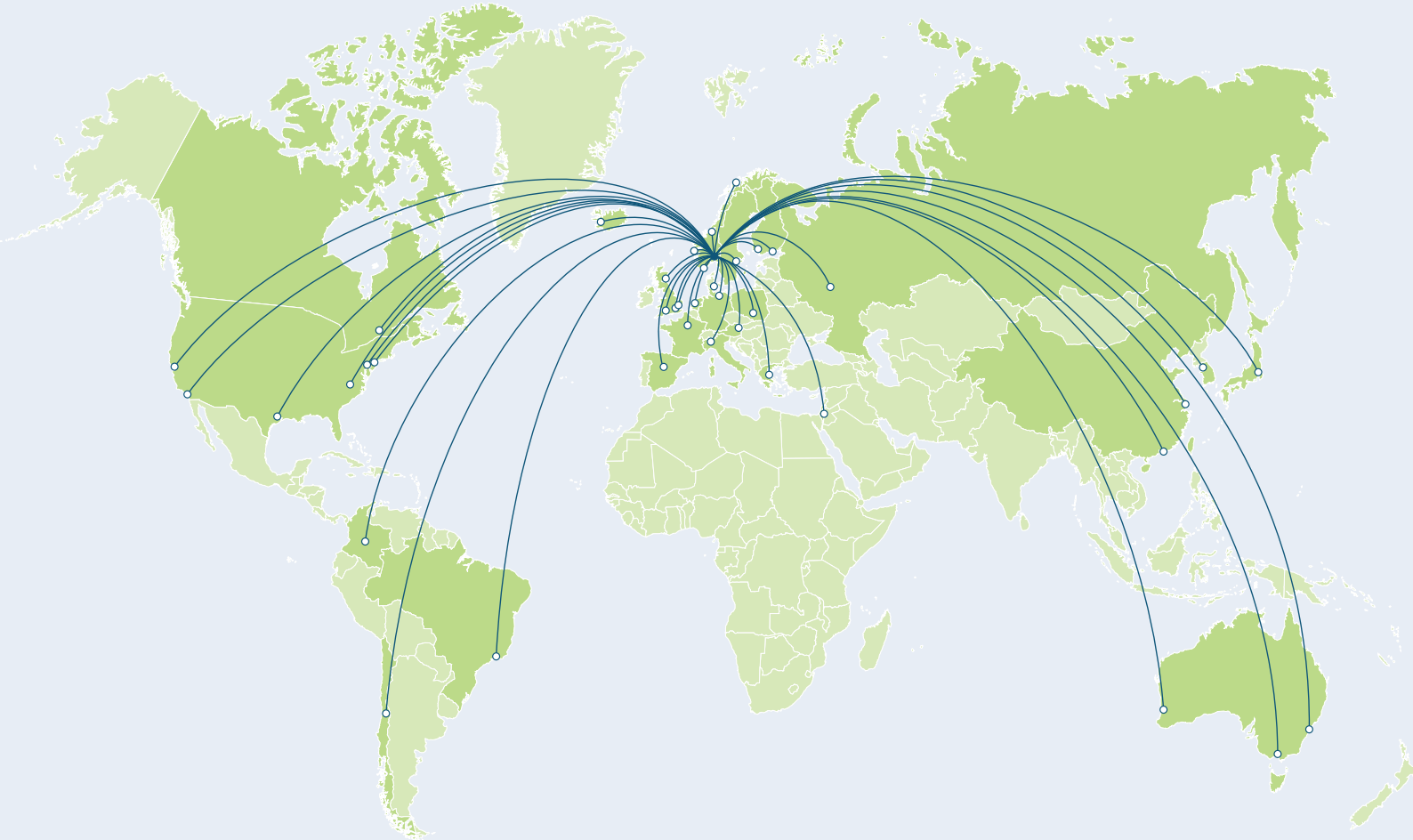
IMPACT FACTOR DISTRIBUTION 2018

52 JOURNAL ARTICLES

73 CeFH IN THE MEDIA

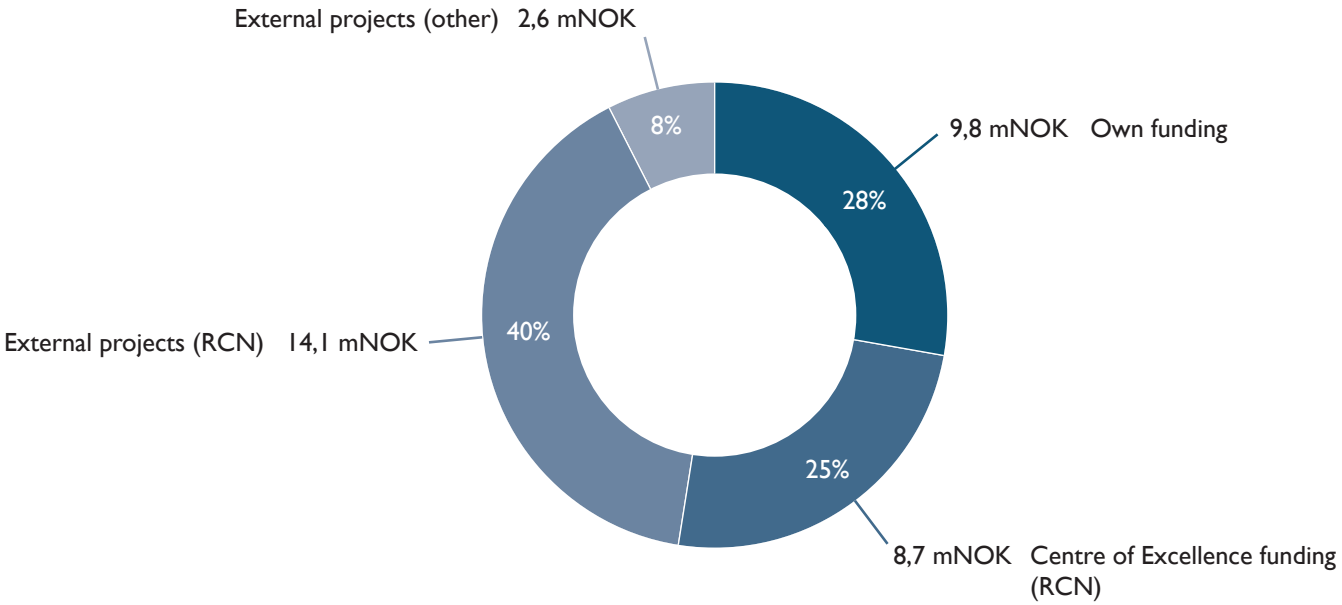
59 CONFERENCE PRESENTATIONS

24 COLLABORATING COUNTRIES



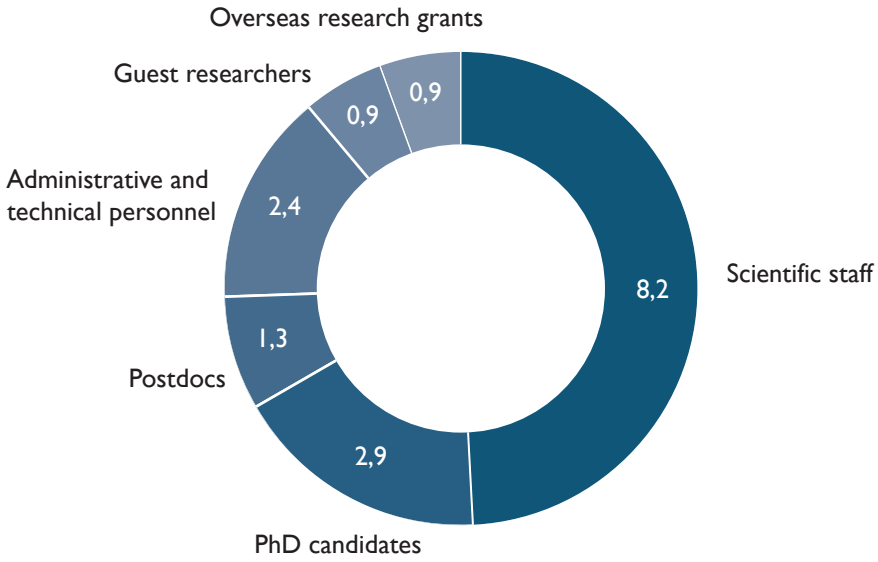
FINANCING 2018

The Centre for Fertility and Health core funding from the Research Council of Norway (RCN) is 136 million Norwegian kroner (mNOK) for the full 10-year period. The last five years are conditional on a positive outcome of the mid-term evaluation. The Norwegian Institute for Public Health contributes with own funding of over 108 mNOK for the 10-year period. In addition, the research activity is financed by other external funding. The figure below shows the distribution of funding in 2018.



FULL-TIME EQUIVALENTS 2018

The figure below shows the distribution of full-time equivalents (FTEs) in the Centre in 2018.



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A new approach to chromosome-wide analysis of X-linked markers identifies new associations in Asian and European case-parent triads of orofacial clefts. Skare Ø, **Gjessing HK, Gjerdevik M,** Haaland ØA, **Romanowska J, Lie RT, Jugessur A**. *PLoS One*. 2017; 12(9): e0183772.

As You Sow, So Shall You Reap: Gender-Role Attitudes and Late-Life Cognition. **Bonsang E**, **Skirbekk V,** Staudinger UM. *Psychological Science* 2017; 28(9): 1201-1213.

SEMINARS 2017-2018

THE CENTRE HAS INITIATED SEVERAL SERIES OF SEMINARS TO FOSTER SCIENTIFIC EXCHANGE.

CeFH Lunch Seminars

Our lunch seminars are informal research seminars that are normally held every Friday. Both researchers at the Centre and researchers from other parts of the world present interesting topics in fertility and health. The presentations include new research ideas, projects, results and methods as well as possible collaborative projects. Although primarily aimed at researchers at the Centre, the seminars are also open to other researchers at the Norwegian Institute of Public Health.

CeFH Genetic Fridays

Genetics Fridays are held every Friday. This is an informal venue for all employees at the Norwegian Institute of Public Health and collaborators who work in genetics, plan to implement genetics in their work, or merely have an interest in genetics. There is room for presentations and/or discussions, where participants can share their knowledge and experience, come up with ideas, and discuss projects and methods.

CeFH Biostatistical Seminars

The biostatistical seminar takes place on a monthly basis. The focus at these seminars is on methods and their mathematical backgrounds. Grant applications may also be presented. We invite a broad range of researchers from Norway and abroad to discuss various topics such as causal inference, Bayesian methods, variable selection, and more. Statisticians and data analysts from the Norwegian Institute of Public Health are invited to join these meetings, as well as people from outside the institute.

Lunch seminars, Genetic Fridays and Biostatistical seminars

Alice Goisis: Effects of parental age. *September 20, 2017*

Rolv Skjærven. *October 11, 2017*

Yunsung Lee: Dynamics of leukocyte telomere length in families. *October 10, 2017*

Jennifer Harris. *November 1, 2017*

Hein Stigum: Sensitivity Analysis Without Assumptions. *November 9, 2017*

Jørg Mørland: LAR-behandling av gravide. *November 15, 2017*

Torkild Hovde Lyngstad: Barnløshet hos menn og kvinner. *December 6, 2017*

Olga Basso: Maternal age at birth and subsequent childlessness in daughters. *December 13, 2017*

Ole Røgeberg: Intelligens og fertilitet. *January 5*

Nina Drange: Eksempler på studier av barnehage og senere effekter, ved bruk av naturlige eksperimenter. *January 19*

Kåre Bævre: Historisk befolkningsregister. *January 26*

Rolv Terje Lie: Prenatal exposure to Chernobyl fallout in Norway: neurological and developmental outcomes in a 25-year follow-up. *February 2*

Jim Oeppen: Fertility indicators. *February 16*

Wendy Sigle: Parental age. *March 16*

Mona Bekkhus: Psykisk helse/stress i svangerskap og barnets helse. *April 27*

Annette Regan: Australian perinatal research and datasources. *May 4*

Yunsung Lee: Mendelian randomization and pleiotropy. *June 1*

Elisabeth Krefting Bjelland: Mammografi data og fruktbarhetsdata. *June 15*

David Leon: Modelling CVD mortality. *August 31*

Sara Cools: Konsekvenser av å få (flere) barn – arbeidsmarked, helse og familiemedlemmers fruktbarhet. *September 7*

Merete Eggesbø and Nina Lousie Torcelino-Iszatt: Miljøgifter og fruktbarhet. *September 14*

Johanna Nader: LifeCycle EU-opportunities to collaborate. *September 21*

Maria Magnus: Estimated risk of miscarriages in Norwegian health registries according to pregnancy history. *October 5*

Lars Christian Stene: Mor og barns gener som påvirker vitamin D status hos nyfødte: resultat fra MoBa og noen simuleringer. *November 2*

Martin Dribe: SES and Fertility in a Global and Historical Perspective. Evidence from Micro-Level Population Dat. *November 16*

Haakon Egdetveit Nustad: Using neighboring correlation to identify differentially methylated regions. *November 16*

Fartein Ask Torvik, Martin Flatø, Camilla Stoltenberg: Health-GAP: Health, maturity, and the gender gap in education. *November 23*

Robyn Wootton: Causal effects of lifetime smoking on risk for depression and schizophrenia: Evidence from a Mendelian randomisation study. *November 23*

Rebecca Lawn: Using Mendelian randomization to answer evolutionary questions: results from MoBa. *November 30*

Rannveig Kaldager Hart: Extended paternity leave, mothers' and fathers' earnings, and union stability. *December 7*

Alexandra Havdahl: The contribution of maternal neurodevelopmental risk alleles to exposures during pregnancy. *December 7*

Anders Huitfeld: The choice of effect measure for binary outcomes: Introducing counterfactual outcome state transition parameters. *December 12*

Simen Markussen: Trends in Assortative Mating and Offspring Outcomes: *December 14*

Martin Tesli: Genome-wide association study of ADHD in MoBa – potentials and challenges. *December 14*

Other CeFH events

Kick-off seminar: October 27, 2017

Allen Wilcox: Using your whole brain – intuition as a research tool

Opening symposium: May 7, 2018

George Davey Smith: What Epidemiologists and Demographers can learn from each other: An Epidemiologist's Perspective

Hans-Peter Kohler: What Epidemiologists and Demographers can learn from each other: A Demographer's Perspective

Opening symposium : May 8, 2018

Tomás Sobotka: Fertility in rich countries: trends, surprises and underlying factors

Torkild Hovde Lyngstad: Fertility and family patterns

Emily Grundy: Reproductive histories and health in mid and later life

George Davey Smith: Can genetics contribute to the study of fertility and health?

Øystein Kravdal: The mortality advantage of the married

Wendy Sigle: Child Outcomes After Parental Separation

Hans-Peter Kohler: Transmission of health across generations

Eric Bonsang: Causal effects of fertility on cognition at older ages

Vegard Skirbekk: New drivers of fertility and implications for health

Allen Wilcox: Prying open the black box of preimplantation loss

Siri Eldevik Håberg: Maternal subfertility and assisted reproductive technologies – implications for parental and child health

CeFH workshops

Collaborations with University of Copenhagen. Visitors: Lone Schmidt and Ditte Vasard. February 9

Effects of paretal age, birth order and birth interval. Visitors: Kieron Barclay, Mikko Myrskylä, Martin Kolk, Katherine Keenan. March 9

Collaborations with FAIR. Visitors: Kjell Gunnar Salvanes, Katrine Vellesen Løken, Aline Bütikofer. September 19.

TEACHING

The researchers at the Centre are involved in many courses organised at various universities.

Håkon Gjessing

- Modern methods for analysing survival and time-to-event data, Nov 2017, (Qualifies for 4 ETCS credit points for PhD students) – NORBIS (National Research School in Bioinformatics, Biostatistics and Systems Biology).
- Genetic epidemiology and genome-wide association analyses, June 2018 (Qualifies for 4 ETCS credit points for PhD students) – NORBIS (National Research School in Bioinformatics, Biostatistics and Systems Biology) - organised togheter with Astanand Jugessur and Rolv Terje Lie.
- Regression models in medical research, 5 credit points, University of Bergen (MEDSTA2).
- Analyses of longitudinal data with Stata, 2 study points, University of Bergen (MEDSTAT3).
- Ultrasound in gynecology and obstetrics step 1, NTNU.

Siri E. Håberg

- Register-based epidemiology, master student course, 3 credit points, University of Oslo.
- Register-based epidemiology/Nordic course in Register based Epidemiology, PhD level, 3 credit points, University of Oslo.
- Nordic course in pharmacoepidemiolgy, PhD level, Karolinska Institutet, Sweden.

Jonas Minet Kinge

- Course in Business Economics, bachelor level, 10 credit points, University of Oslo (HØKON1201) – 2018.

Øystein Kravdal

- Course in Population Health, 10 credit points, combined undergraduate and graduate level, University of Oslo (ECON 3725/4725) – spring 2018.
- Course in Basic Demography, 10 credit points, undergraduate level, University of Oslo (ECON 1710) – autumn 2018.

Per Magnus

- Course in clinical, epidemiological and public health research, 5 credit points, University of Oslo (MF9230), arranged triannually.

Fartein Ask Torvik

- 10 credit point bachelor level course in empirical research methods at the University of Oslo (PSY1010/PSYC1100) – University of Oslo - 2018

Anders Skrondal

- Multilevel and Longitudinal Modeling (UV9257U), University of Oslo. PhD level. 80 participants from 7 countries - 2018.
- Research Group on Multilevel Modeling, University of California, Berkeley (EDUC 275H) – Spring 2018.
- Research Group on Multilevel Modeling, University of California, Berkeley (EDUC 275H) – Fall 2018.

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