# Impact case guidelines

Each case study should include sufficiently clear and detailed information to enable the evaluation committee to make judgements based on the information it contains, without making inferences, gathering additional material, following up references or relying on members' prior knowledge. References to other sources of information will be used for verification purposes only, not as a means for the evaluation committee to gather further information to inform judgements.

In this evaluation, impact is defined as an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia.

**Timeframes**
- The impact must have occurred between 2012 and 2022
- Some of the underpinning research should have been published in 2012 or later
- The administrative units are encouraged to prioritise recent cases

**Page limit**
Each completed case study template will be limited to **five pages** in length. Within the annotated template below, indicative guidance is provided about the expected maximum length limit of each section, but institutions will have flexibility to exceed these so long as the case study as a whole remains no longer than **five pages** (font Calibri, font size 11). Please write the text into the framed template under the sections 1–5 below. The guiding text that stands there now, can be deleted.

**Maximum number of cases permitted per administrative unit**
For up to 10 researchers: one case; for 10 to 30 researchers: two cases; for 30-50 researchers: three cases; for 50-100 researchers: four cases, and up to five cases for units exceeding 100 researchers.

**Naming and numbering of cases**
Please use the standardised short name for the administrative unit, and the case number for the unit (1,2,3, etc) in the headline of the case. Each case should be stored as a separate PDF-document with the file name: [Name of the institution and name of the administrative unit] [case number]

**Publication of cases**
RCN plans to publish all impact cases in a separate evaluation report. By submitting the case the head of the administrative units consents to the publication of the case. Please indicate below if a case may not be made public for reasons of confidentiality.

*If relevant, describe any reason to keep this case confidential:*

N/A

# [University of Oslo, Institute of Basic Medical Sciences] [case number 1]

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| **Institution: University of Oslo (UiO)** |
| **Administrative unit: Institute of Basic Medical Sciences (IMB)** |
| **Title of case study: 4D epigenetics of adipose tissue stem cells** |
| **Period when the underpinning research was undertaken: 2014-2022** |
| **Period when staff involved in the underpinning research were employed by the submitting institution: 2009-2022** |
| **Period when the impact occurred: 2014-2022** |

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| **1.Summary of the impact** (indicative maximum 100 words)<br>In a worldwide context of obesity, much as long remained unknown on principles of genome organization which govern fat stem cell differentiation into adipocytes. We describe a scientific impact on the 4-dimensional (4D; space-time) organization of the adipose stem cell and adipocyte genome. We have identified a new level of spatial chromatin organization, and henceforth have unveiled contributions of two main chromatin organizers to the 4D genome, and their significance in pathophysiological contexts. We have generated and made publicly available epigenomic datasets and bioinformatics pipelines which constitute valuable resources for the scientific community. |
| **2. Underpinning research** (indicative maximum 500 words)<br>The discovery in the early 2000s that adipose tissue stem cells (ASCs) could be isolated from fat tissue has sparked research worldwide on understanding and harnessing their differentiation potential into adipocytes and other cell types. In the same decade, the explosion of transcriptomics and other genomics technologies has enabled unprecedented space-resolved studies of genome (chromatin) organization.<br>ASCs, isolated from human adipose tissue as a by-product of liposuction, constitute a powerful system to study adipogenesis. Using this system, we and other groups have revealed i) changes in the transcriptome, the 3D genome and chromatin accessibility to transcription factors, ii) acquisition of new epigenetic states, and iii) remodeling of interactions between gene promoters and enhancers.<br>3D chromatin conformation can change in response to external signals during development, differentiation and tissue homeostasis. This view rests on discoveries of genomic elements and nuclear architectural proteins that structurally shape the genome at multiple levels. At the largest scale, chromosomes are organized in territories broadly divided into euchromatic and transcriptionally active A compartments, and heterochromatic and overall inactive B compartments. Within compartments, topologically-associated domains (TADs) of higher chromatin contact frequencies are important for gene expression regulation, and, as we and others have shown (including in this impact case), establish long-range contacts with other TADs, shaping high-order chromatin architecture. In addition, radial (center-to-periphery) genome organization relies on associations of chromatin with the nuclear lamina, at the nuclear envelope, via lamina-associated domains (LADs). Some LADs change during differentiation or are altered in disease states, and laminopathies, diseases caused by mutations in nuclear lamin A, underscore the importance of maintaining a proper genome organization.<br>In this context, we have established a research program aiming to map and decipher the genome-wide epigenetics underlying the differentiation potential of ASCs. We have provided evidence of contributions from two main genome organizers (TADs and LADs) to the 4D conformation of chromatin (i.e. in 3D over time), and of their significance in laminopathies. We have made available epigenomic datasets and bioinformatics pipelines, which constitute resources for the scientific community.<br>The work has largely been undertaken in the Stem Cell Epigenetics Laboratory ([www.collaslab.org](www.collaslab.org)), part of the Chromatin Biology research group at IMB. The lab has counted 12- |

18 people at any time in the 2012-2022 period, and has benefitted from interactions with other groups at IMB and internationally. Through publications and dissemination activities, the impact has occurred continuously throughout the 2013-2022 period, but has culminated in 2029-2022.

Key researchers, dates in the administrative unit, and position:

- Philippe Collas (1999-present), researcher then (2003 -) Professor, Head of research group Head of Department (2016-)
- Julia Madsen-Østerbye (2019-present), postdoc
- Nolwenn Briand (2017-present), postdoc then researcher
- Natalia Galigniana (2021-present), postdoc
- Aurélie Bellanger (2018-present), postdoc then researcher
- Jonas Paulsen (2016-2020), postdoc
- Annael Brunet (2016-2020), postdoc
- Erwan Delbarre (2006-2018), postdoc then researcher
- Anja Oldenburg (2009-2018), researcher
- Evdokiia Potolitsyna (2018-2021), PhD student
- Tharvesh Liyakat-Ali (2016-2020), PhD student
- Frida Forsberg (2017-2020), PhD student
- Jane Spirkoski (2014-2017), PhD student
- Akshay Shah (2014-2017), PhD student
- Torunn Rønningen (2013-2016), PhD student
- Eivind Lund (2013-2015), PhD student
- Engineers in the lab (Anita Sørensen, Kristin Vekterud, Mohamed Abdelhalim [bioinfo])

Relevant key contextual information about this area of research:

Worldwide, over 2 billion adults are overweight, including 1 billion clinically obese. Adipose tissue has there become a major research focus because of its capacity to store energy in the form of lipids in white adipocytes, and dissipate energy by heat in thermogenic adipocytes. In parallel, the past decade has witnessed an explosion of genomics methods enabling studies of regulation of gene expression and cell fate at unprecedented levels, notably (and critical to this research) in the 3D context of genome organization.

**3. References to the research** (maximum six references):

- Madsen-Østerbye J, Abdelhalim M, Baudement MO, Collas P. 2022. Local euchromatin enrichment in lamina-associated domains anticipates their repositioning in the adipogenic lineage. Genome Biol 23, 91. https://pubmed.ncbi.nlm.nih.gov/35410387/
- Paulsen J, Liyakat Ali TML, Nekrasov M, Delbarre E, Baudement, MO, Kurscheid S, Tremethick D, Collas P. 2019. Long-range interactions between topologically-associating domains shape the 4-dimensional genome during differentiation. Nature Genet 51, 835-843. https://pubmed.ncbi.nlm.nih.gov/31011212/
- Paulsen J, Ali TML, Collas P. 2018. Computational 3D genome modeling using Chrom3D. Nature Protoc 13, 1137-1152. https://pubmed.ncbi.nlm.nih.gov/31011212/
- Paulsen J, Sekelja M, Oldenburg AR, Barateau A, Briand N, Delbarre E, Shah, A, Sørensen AL, Vigouroux C, Buendia B, Collas P. 2017. Chrom3D: three-dimensional genome modeling from Hi-C and nuclear lamin-genome contacts. Genome Biol 18, 21-29. https://pubmed.ncbi.nlm.nih.gov/28137286/
- Oldenburg AR, Briand N, Sørensen AL, Cahyani I, Shah A, Moskaug JØ, Collas P. 2017. A lipodystrophy-causing lamin A mutant alters conformation and epigenetic regulation of the anti-adipogenic MIR335 locus. J Cell Biol 216, 2731-2743. https://pubmed.ncbi.nlm.nih.gov/28751304/

- Lund E.G., Oldenburg A., Collas P. 2014. Enriched domain detector: a program for detection of wide genomic enrichment domains robust against local variations. Nucl. Acids Res. 42, e92. https://pubmed.ncbi.nlm.nih.gov/24782521/

**4. Details of the impact** (indicative maximum 750 words)

*The 3-dimensional epigenome of fat stem cells and adipocytes in health and disease*

Cell fate decisions are programmed at several levels of gene expression, including heritable epigenetic modifications. Interactions between chromosomes, and repositioning of genes in the 3D nucleus space, provide a blueprint of temporal gene expression. Aspects of 3D genome organization are regulated in a 4D space where the 4th dimension is time. Nutrient availability also modulates the epigenome, providing another level of complexity of gene regulation and cell fate, particularly in cells from adipose tissue. This case study has over 10 years looked into mechanistic links between a changing 3D chromatin landscape, gene expression and adipose cell metabolic state and function, in health and pathological conditions (lamin A-linked lipodystrophies).

Omics technologies enable investigations of structural properties of the genome in space. As suitable molecular and bioinformatics approaches were lacking to deeply investigate radial genome architecture, we have tailored chromatin assays and developed a bioinformatics pipeline (Enriched Domain Detector; https://github.com/CollasLab/edd) for analyses of interactions of chromatin with the nuclear lamina. We have then developed a 3D genome modeling tool, Chrom3D (https://github.com/CollasLab/Chrom3D; published in *Genome Biology* in 2017 and *Nature Protocols* in 2018) to infer new principles of 3D genome organization, and this can go awry in lamin A-linked lipodystrophies.

Using as model system differentiation of human ASCs into adipocytes, we have combined genomics and computational approaches to show in a 2019 landmark *Nature Genetics* paper that long-range assemblies of topological domains (TADs), which we called TAD cliques, shape the 4D genome during adipogenesis. A relationship between TAD cliques and LADs suggests that cliques stabilize heterochromatin at the nuclear periphery. This and related work show that TAD cliques represent a new level of 4D genome conformation reinforcing the silencing of developmental genes. In a collaboration with Stanford U, we have applied Chrom3D to show that carcinogen susceptibility lies at the origin of genome instability regulated by nuclear architecture. Implementing theoretical physics, we have in parallel used polymer simulations to provide new insights on the physical properties of chromatin affect its interaction with the nuclear lamina. From this, we have investigated how LADs impinge on adipogenic gene expression. Gains and losses of LADs are prominent features of adipogenic chromatin rearrangement, in that LADs sequester genes irrelevant for fat cell function, while important genes are released from the lamina. Our work also emphasizes a challenging concept of epigenetic heterogeneity at the nuclear lamina. LADs emerge as central features of adipose nuclear architecture which contribute to reinforcing adipose cell type identity.

Chromatin organization in lamin A-linked lipodystrophies. A-type lamins integrate metabolic signals and convey them to the genome. Investigating metabolic aspects of genome organization, we have shown that a lipodystrophy (FPLD2)-causing host-spot lamin A mutation alters conformation and epigenetic regulation, resulting in a loss-of-function of differentiation-dependent lamin A binding to chromatin. This links a laminopathy-causing mutation to an unsuspected deregulation of spatial chromatin conformation, impacting adipose stem cell fate. Using induced pluripotent stem cells derived from FPLD2 patient's fibroblasts, we have connected a lipodystrophic lamin A mutation to defective endothelial differentiation, and propose that the mutation rewires the fate of several lineages, resulting in multi-tissue pathogenic phenotypes.

Our results have impacted science mainly because we have identified a new level of spatial chromatin organization; in doing so we have unveiled contributions of two main genome organizers to the 4D genome (LADs and TAD cliques) and their significance in pathophysiological

contexts. We have generated and made publicly available epigenomic datasets and two bioinformatics pipelines which constitute valuable resources for the scientific community.

How has the process led to the impact:
Wet-lab methods, computational tools and results have been presented at conferences and research institutions (upon invitation) worldwide.  They have resulted in the group being contacted for collaborations, tutorials, and wide use by research labs worldwide who also have published using these methods and tools. This case study has amply complemented research at IMB, notably in molecular nutrition, adipose and lipid biology, and clinical nutrition on hypercholesterolemia and childhood obesity, in the Department of Nutrition.

Beneficiaries, nature of the impact:
The primary beneficiaries of the impact are members of the scientific community, given the basic nature of the findings. Significance for industry has been indirect, as our wet-lab methods, computational tools, and researchers who have graduated from the group, have generated strong interest in the biotech sector. Societal significance has to date however been limited due to the very basic nature of the work. Our dissemination plan has included publications in high-ranked journals, reviews, seminars, public lectures, presentations to patient groups at European congresses, and social media. Impact has also been tremendous regarding the amount of funding it has generated, notably from the Research Council of Norway, with at least 5 Research Council projects related to the case study, and 3 PhD and Postdoc stipends plus 1 program grant from Helse Sør-Øst (Norwegian Health Authorities), 3 EU-UiO Scientia fellows, and 1 EAA grant (NO-CZ).

Indicators of impact extent (2013-2022):
- No. Pubmed publications directly related to the impact: 46
- No. Github-released bioninformatics tools: 2
- No. speaker invitations at national and international conferences: 57
- No. speaker invitations at Universities and Institutes worldwide: 44

**5. Sources to corroborate the impact** (indicative maximum of ten references)
- Potolitsyna E, Hazell Pickering S, Germier T, Collas P, Briand N. 2022. Long non-coding RNA HOTAIR regulates cytoskeleton remodeling and lipid storage capacity during adipogenesis. Sci Rep 12, 10157
- Brunet A, Destainville N, Collas P. 2021 Physical constraints in polymer modeling of chromatin associations with the nuclear periphery at kilobase scale. Nucleus 12, 6-20
- Brunet A, Forsberg F, Fan Q, Sæther T, Collas P. 2019. Nuclear lamin B interactions with chromatin during the circadian cycle are uncoupled from periodic gene expression. Front Genet 10, 917
- Briand N, Guénantin AC, Jeziorowska D, Shah A, Mantecon M, Capel E, Garcia M, Oldenburg A, Paulsen J, Hulot JS, Vigouroux C, Collas P. 2018. The lypodystrophic hotspot lamin A p.R482W mutation deregulates the mesodermal inducer T/Brachyury and early vascular differentiation gene networks. Hum Mol Genet 27, 1447-1459
- Delbarre, E, Ivanauskiene K, Spirkoski J, Shah A, Vekterud K, Moskaug JØ, Bøe SO, Wong L, Küntziger T, Collas P. 2017. PML protein organizes heterochromatin domains where it regulates histone H3.3 deposition by ATRX/DAXX. Genome Res. 27, 913-921
- Rønningen T., Shah A, Oldenburg AR, Vekterud K, Delbarre E, Moskaug JØ, Collas P. 2015. Prepatterning of differentiation-driven nuclear lamin A/C-associated chromatin domains by GlcNAcylated histone H2B. Genome Res 25, 1825-1835
- Shah, A., Oldenburg, A.R., Collas, P. 2014. A hyper-dynamic nature of bivalent promoter states underlies coordinated developmental gene expression modules. BMC Genomics 15, 1186

- Ivanauskiené K., Delbarre E., McGhie J.D., Küntziger T., Wong L.H., Collas P. 2014. The PML-associated protein DEK regulates the balance of H3.3 loading on chromatin and is important for telomere integrity. Genome Res. 24, 1584-1594
- Lund E.G., Oldenburg A., Collas P. 2014. Enriched domain detector: a program for detection of wide genomic enrichment domains robust against local variations. Nucl. Acids Res. 42, e92
- Oldenburg A.R., Delbarre E., Thiede B., Vigouroux C., Collas P. 2014. Deregulation of Fragile X-related protein 1 by the lipodystrophic lamin A p.R482W mutation elicits a myogenic gene expression program in preadipocytes. Hum. Mol. Gen. 23, 1151-1162
- Lund E., Oldenburg A.R., Delbarre E., Freberg C.T., Duband-Goulet I., Eskeland R., Buendia B., Collas P. 2013. Lamin A/C-promoter interactions specify chromatin state-dependent transcription outcomes. Genome Res. 23, 1580-1589

# [University of Oslo, Institute of Basic Medical Sciences] [case number 2]

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| **Institution: University of Oslo (UiO)** |
| **Administrative unit: Institute of Basic Medical Sciences (IMB)** |
| **Title of case study: The role of sleep in brain waste clearance** |
| **Period when the underpinning research was undertaken: 2010–2022** |
| **Period when staff involved in the underpinning research were employed by the submitting institution: 2006–present** |
| **Period when the impact occurred: 2012–2022** |

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| **1. Summary of the impact** (indicative maximum 100 words)<br>Research by the group of the late Professor Erlend Nagelhus and his successor Associate Professor Rune Enger at Department of Molecular Medicine, Institute of Basic Medical Sciences has contributed to ground-breaking discoveries that have increased our understanding of how the brain rids itself of harmful waste. Apart from a substantial academic impact, the findings have paved the way for foundational and applied research across the globe and in collaborating groups in the clinic that has changed patient diagnostics of brain fluid disorders. Moreover the findings have increased public awareness of the importance of sleep for brain health neurodegeneration in the general public. |

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| **2. Underpinning research** (indicative maximum 500 words)<br>In 2012 Professor Nagelhus had a central contribution to a milestone paper by Professor Maiken Nedergaard in Rochester, NY, USA. They demonstrated that the cerebrospinal fluid flows along the brain's vasculature, and that this flow contributes to the clearance of waste products from the brain, and is dependent on water channels – *Aquaporins* – in perivascular astrocyte endfoot processes. The system was coined 'the glymphatic system', due to its functional analogy to the lymphatic system in the rest of the body, and its dependency on the astrocyte subtype of glial cells. The system was shown to remove for instance amyloid beta from the brain and thus may play a role in preventing neurodegenerative disease. In 2013 follow-up work in the Nedergaard lab demonstrated that this system primarily is active in sleep.<br><br>The original reports on the glymphatic system from the Nedergaard lab were enabled by use of advanced in vivo optical imaging techniques called two-photon microscopy. In Oslo, Nagelhus and his group had established similar technology and were refining this technique over the next decade to enable studies in naturally sleeping head-fixed mice, to try to elucidate mechanisms that regulate the glymphatic system. A key step was establishing in vivo two-photon microscopy in anesthetised and later unanesthetized mice. Then PhD student (2013–2016) and later postdoctoral researcher (2016–2019), and finally associate professor Rune Enger had the prime responsibility of establishing these techniques in the group. This led to the first study using genetically encoded Ca$^{2+}$ sensors in both astrocytes and neurons at the same time in a single preparation in (Enger et al 2017, Cerebral Cortex). Laura Bojarskaite (PhD student 2015–2020, now a senior postdoctoral researcher in the group) had the major responsibility of setting up two-photon microscopy of naturally sleeping head fixed mice. Concurrently, PhD students Daniel M. Bjørnstad (PhD student from 2016-2022) and Knut S. Åbjørsbråten (PhD student from 2016 to 2022) under supervision of Enger developed a pipeline of data analyses of two-photon imaging data, tailored for natural sleep, including novel methods for analysing astrocytic signalling. In January 2020, Nagelhus tragically passed away. Subsequently, under Enger's leadership, the first description of astrocyte signalling in natural sleep was published (Bojarskaite&Bjørnstad et al, Nat Comm 2020). These findings may be important for regulating the glymphatic system, and the study suggested a salient role of astrocytes in maintaining uninterrupted deep sleep. Following up on this work, Enger and his team pursued brain waste clearance |

mechanisms in sleep, demonstrating for the first time the dynamics of the vasculature and surrounding endfeet in natural sleep in *Nature Communications* in 2023 (Bojarskaite&Vallet&Bjørnstad et al, Nat Comm 2023).

**3. References to the research** (indicative maximum of six references)

Iliff, J.J., Wang, M., Liao, Y., Plogg, B.A., Peng, W., Gundersen, G.A., Benveniste, H., Vates, G.E., Deane, R., Goldman, S.A., Nagelhus, E.A. and Nedergaard, M., 2012. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Science translational medicine, 4(147), pp.147ra111-147ra111.https://doi.org/10.1126/scitranslmed.3003748

Rune Enger, Didrik B. Dukefoss, Wannan Tang, Klas H. Pettersen, Daniel M. Bjørnstad, P. Johannes Helm, Vidar Jensen, Rolf Sprengel, Koen Vervaeke, Ole P. Ottersen, Erlend A. Nagelhus, Deletion of Aquaporin-4 Curtails Extracellular Glutamate Elevation in Cortical Spreading Depression in Awake Mice, Cerebral Cortex, Volume 27, Issue 1, January 2017, Pages 24–33. https://doi.org/10.1093/cercor/bhw359

Bjørnstad, Daniel M., Knut S. Åbjørsbråten, Eivind Hennestad, Céline Cunen, Gudmund Horn Hermansen, Laura Bojarskaite, Klas H. Pettersen, Koen Vervaeke, and Rune Enger. 2021. "Begonia—A Two-Photon Imaging Analysis Pipeline for Astrocytic Ca$^{2+}$ Signals." Frontiers in Cellular Neuroscience 15: 176. https://doi.org/10.3389/fncel.2021.681066

Bojarskaite, Laura, Daniel M. Bjørnstad, Klas H. Pettersen, Céline Cunen, Gudmund Horn Hermansen, Knut Sindre Åbjørsbråten, Anna R. Chambers, et al. 2020. "Astrocytic Ca$^{2+}$ Signaling Is Reduced during Sleep and Is Involved in the Regulation of Slow Wave Sleep." Nature Communications 11 (1): 1–16. https://doi.org/10.1038/s41467-020-17062-2

Knut Sindre Åbjørsbråten, Gry HE Syverstad Skaaraas, Céline Cunen, Daniel M Bjørnstad, Kristin M Gullestad Binder, Laura Bojarskaite, Vidar Jensen, Lars NG Nilsson, Shreyas B Rao, Wannan Tang, Gudmund Horn Hermansen, Erlend A Nagelhus, Ole Petter Ottersen, Reidun Torp, Rune Enger (2022) Impaired astrocytic Ca2+ signaling in awake-behaving Alzheimer's disease transgenic mice eLife 11:e75055 https://doi.org/10.7554/eLife.75055

Bojarskaite, Laura, Alexandra Vallet, Daniel M. Bjørnstad, Kristin M. Gullestad Binder, Céline Cunen, Kjell Heuser, Miroslav Kuchta, Kent-Andre Mardal, and Rune Enger. 2023. "Sleep Cycle-Dependent Vascular Dynamics in Male Mice and the Predicted Effects on Perivascular Cerebrospinal Fluid Flow and Solute Transport." Nature Communications 14 (1): 953. https://doi.org/10.1038/s41467-023-36643-5

**4. Details of the impact** (indicative maximum 750 words)

Professor Nagelhus as part of the research environment led by Professor Ole Petter Ottersen in Oslo demonstrated in the late 1990s the location of aquaporin-4 water channels in the astrocytic endfeet in the central nervous system. This interest and the development of aquaporin-4 knockout mouse lines laid the groundwork for the work leading up to the first description of the glymphatic system in 2012. The discovery and publication of the glymphatic system as a way the brain rids itself of waste products in *Science Translational Medicine* received some attention, but it was only the year after when this system was found to be considerably more active in sleep than wakefulness that a lot of attention was given to this line of research. The paper (Xie et al 2013, *Science*) demonstrating that the glymphatic system is active in sleep and certain types of anaesthesia was highlighted as one of the top ten scientific breakthroughs of 2013 by *Science Magazine* and opened up a new field of research. The paper was picked up by a range of international news outlets and was proposed to be an explanation of the universal need for sleep: for the brain to rid itself of harmful waste products. Importantly it was shown that beta-amyloid, an important player in Alzheimer's disease and other

neurodegenerative disorders, is cleared by the glymphatic system, linking the amount and quality of sleep with a potential future risk of neurodegenerative disease. This whole research field that sprung out of the interest of aquaporins in astrocytes in the brain and collaboration with Maiken Nedergaard is a very active field of research that has already changed diagnostics, but potentially will also change treatment for a range of brain disorders in the not too distant future. Today, a Pubmed search of 'glymphatic' reveals around 1500 articles, and a number of patents aimed for treatment of human disease have been registered.

Nagelhus' role in the original descriptions of the glymphatic system received a lot of attention in Norway, both in academia and in the general population, and spurred an interdisciplinary research effort in Oslo studying the glymphatic system with clinical, neuroimaging, and biophysical modelling approaches. Importantly, this work led to the first study demonstrating the glymphatic system in humans using intrathecal MRI contrast by collaborators Professor Per Kristian Eide and Dr. Geir Ringstad at Oslo University Hospital (Eide & Ringstad, Acta Radiologica Open 2015). This new imaging modality has now changed patient diagnostic procedures for patients with normal pressure hydrocephalus, where tracer clearance distribution is used as a means to quantify CSF flow disturbances in these patients.

Following the initial papers on the Glymphatic system, Nagelhus established infrastructure and know-how to further study the sleeping brain. To establish optical imaging of natural sleep in rodents represented a challenge. The initial steps included establishing in vivo microscopy at the lab in Oslo, and extending these imaging models to the study of unanesthetized mice. After Nagelhus' passing in 2020, associate professor Rune Enger led the further development of the research. In 2020 Enger and his lab were able to for the first time describe astrocytic signalling across the natural sleep-wake state of mice. The paper was published in *Nature Communications* and listed as Editor's pick of the month. Importantly, these signalling mechanisms across the sleep-wake state could be a part of the explanation of how the glymphatic system is regulated. The results received broad recognition in the field, and in the general population: news outlets like *Verdens Gang* (the largest newspaper in Norway) reported the study, raising awareness of the importance of sleep for proper brain functioning. The authors were invited to contribute to a range of public outreach events where focus has been to raise public awareness on the detrimental effects of sleep loss on brain health. The group also featured in *Solaris Naturfag* 3–4 textbook for elementary school, raising awareness of the need for sleep in children, an important public health focus given the potential detrimental effects of personal smart devices and social media.

In the following years, the group continued investigating mechanisms underpinning the glymphatic system and were for the first time able to show in 2023 that sleep-specific dynamics of the arteries and arterioles of the brain serve as pumps that likely drives fluid and solute movement in the brain in sleep. The study was a collaboration with Simula Research Laboratory and Department of Mathematics at UoO and published in *Nature Communication* in 2023. These findings could explain how brain health and vascular health seems to both strongly correlate with Alzheimer's dementia. The findings received widespread attention in the news and through various popular science outlets, including the front page and 2 full pages in *Verdens gang*, as well as radio interviews in NRK EKKO, national radio.

**5. Sources to corroborate the impact** (indicative maximum of ten references)

Kaalstad, Jørn. 2023. "Kan Hindre Alzheimers." Verdens Gang, March 25, 2023.

Kingsrød, Marie Golimo. 2020. "Søvnmysteriet." Verdens Gang, September 7, 2020.

"Astrocytes Help to Maintain Slow Wave Sleep" Neuroscience News, July 15, 2020
https://neurosciencenews.com/astrocytes-slow-waves-sleep-16652/

"Astrocytes Play an Important Role in Maintaining Slow Wave Sleep" Technology Networks, August 5, 2020.
https://www.technologynetworks.com/neuroscience/news/astrocytes-play-an-important-role-in-maintaining-slow-wave-sleep-338295

"Dementia and Sleep: It's Not Just Deep Sleep That Counts" in the podcast The Snooze Button by Neil Hedley with Laura Bojarskaite, PhD. September 7, 2020.

Isachsen, Henriette Bertheussen. 2023. "Norsk studie kan bidra til å forebygge Alzheimers: Fant at søvn gir mer effektiv «hjernevask»", Dagens Medisin, April 3, 2023.
https://www.dagensmedisin.no/alzheimers-sykdom-forskning-universitetet-i-oslo-uio/norsk-studie-kan-bidra-til-a-forebygge-alzheimers-fant-at-sovn-gir-mer-effektiv-hjernevask/558638

Munkebye, E., K. Skage, and A. Munkebye. "Solaris-Naturfag (3-4)." (2022): "Hvorfor må vi sove?", s. 131.

Laura Bojarskaite on Lithuanian national TV morning show "good morning" talking about the research in the research group
https://www.lrt.lt/mediateka/irasas/2000211890/neuromokslininke-musu-smegenys-keiciasi-ir-del-skirtingu-metu-laiku-ir-sviesos-kiekio?fbclid=IwAR1zLZDRUlA2slgoibV5KO1MA8WU06PGbRnIbQdsKHZQM_eACPhJvU2Araw

NRK EKKO, "Hjerneforskere får millioner til Alzheimerforskning"
https://radio.nrk.no/program/MDFP02018123

Public outreach through Hjernehelsekonferansen og Hjernerådet:
https://www.hjerneradet.no/hapet-pa-1000-svar-har-hittil-fatt-18-000-2-2-4-2-4/

# [University of Oslo, Institute of Basic Medical Sciences] [case number 3]

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| **Institution: University of Oslo (UiO)** |
| **Administrative unit: Institute of Basic Medical Sciences (IMB)** |
| **Title of case study: Prevention of non-communicable diseases (NCDs) by promoting a healthy diet among children** |
| **Period when the underpinning research was undertaken: 2012-2022** |
| **Period when staff involved in the underpinning research were employed by the submitting institution: 2007-2022** |
| **Period when the impact occurred: 2013-2022** |

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| **1. Summary of the impact** (indicative maximum 100 words) |
| Several researchers at IMB have for many years focused their research on prevention of non-communicable diseases (NCDs) by promoting a healthy diet. Establishing healthy dietary habits early in life can promote a healthy diet throughout life. The results from our research have had an important academic impact. Additionally, the results add essential knowledge to nutritional policy and implementation of diet-related guidelines, which are developed by the Norwegian Directorate of health. Thus, this impact case describes our research's social impact on policy and public health. Moreover, the findings have increased public awareness of the importance of healthy dietary habits early in life. |
| **2. Underpinning research** (indicative maximum 500 words) |
| Together with the Norwegian Institute of Public Health/Directorate of Health, Prof Frost Andersen regularly conduct **national dietary surveys**. The most recent surveys among children aged 9 and 13 years (UNGKOST 3 rapport, 2015) showed that children ate too much saturated fat and added sugar, and they ate less fruit, vegetables and fish than recommended. This is a dietary pattern, which is associated with increased risk of obesity and cardiovascular diseases (CVD). In the project**, the BRA-study** funded by the Research Council of Norway, profs. Lien and Frost Andersen et al. aimed to increase vegetable intake among 3–5-year-olds by changing the food environment in the kindergartens and at home. Important non-academic partners were the Information bureau for fruit and vegetables and Geitmyra culinary centre for children. There were no significant differences in the parent reported vegetable intake of the children the intervention and control groups, but the amount of vegetable consumed in the intervention kindergartens were higher than the control group. There were also greater amounts and variation in vegetables served in the intervention kindergartens, but there were no changes at home.  In the project "**The school as a public health actor: Strategies for successful implementation of guidelines for food and meals**" funded by the Research Council of Norway and the Norwegian Directorate of Health, the focus on shaping the food environment of children by public policy was further studied by Prof Lien et al. A questionnaire for measuring guidelines adherence was developed. Theory-guided qualitative interviews revealed several factors affecting guideline implementation at macro, school, and individual levels. The project RØRE (Move) in the county of Østfold was an important non-academic partner. |
| The national dietary surveys also include infants and small children (spedkost and småbarnskost). Prof. Holven et al., conducted a **sub study to investigate the prevalence of elevated cholesterol levels among infants and small children**. The study was funded by IMB and Throne Holst foundation for nutrition research, UiO. They found a large variation in plasma cholesterol levels in infants and small children aged 6, 12 ad 24 months, and 20% of these infants had total cholesterol above 5 mmol/l which is the current recommended level. The cholesterol levels at 6 and 12 months were significantly correlated, and other studies have shown that the cholesterol levels track further through life meaning that children with high cholesterol will become adults with high cholesterol |

and these children will therefore have a higher risk for CVD later in life unless lifestyle changes are made.

References to the research (indicative maximum of six references)

1. Iodine intake among children and adolescents in Norway: Estimates from the national dietary survey Ungkost 3 (2015-2016).Medin AC, Carlsen MH, Andersen LF**.**J Trace Elem Med Biol. 2020 Mar;58:126427. doi: 10.1016/j.jtemb.2019.126427.

2. Effects of a kindergarten intervention on vegetables served and staff's food-related practices: results of a cluster randomised controlled trial - the BRA study.
Himberg-Sundet A, Kristiansen AL, Frost Andersen L, Bjelland M, Lien N. Public Health Nutr. 2020 Apr;23(6):1117-1126.

3. Kristiansen, Anne Lene; Bjelland, Mona; Himberg-Sundet, Anne; Lien, Nanna; Holst, René & Andersen, Lene Frost (2019). Effects of a cluster randomized controlled kindergarten-based intervention trial on vegetable consumption among Norwegian 3–5-year-olds: the BRA-study. BMC Public Health. ISSN 1471-2458. 19(1), s. 1–10. doi: 10.1186/s12889-019-7436-3.

4. Randby, Jorunn Sofie; Meshkovska, Biljana; Holbæk, Helene & Lien, Nanna (2021). An Exploration of Implementation Enablers and Barriers for Norwegian School Meal Guidelines. Global Implementation Research and Applications. ISSN 2662-9275. 1, s. 122–134. doi: 10.1007/s43477-021-00010-7.

5. Cholesterol at ages 6, 12 and 24 months: Tracking and associations with diet and maternal cholesterol in the Infant Cholesterol Study. Øyri LKL, Bogsrud MP, Kristiansen AL, Myhre JB, Astrup H, Retterstøl K, Brekke HK, Roeters van Lennep JE, Andersen LF, Holven KB. Atherosclerosis. 2021 Jun;326:11-16. doi: 10.1016/j.atherosclerosis.2021.04.017.

**4. Details of the impact** (indicative maximum 750 words)

An unhealthy diet is one of the major causes of NCDs, and overweight/obesity is a direct risk factor for many NCDs, including CVDs. In addition, it is well known that plasma cholesterol is an important risk factor for CVD. Although diet is an individual behaviour, there is an increased recognition that this behaviour to a great extent is driven by an unhealthy food environment and that policies should target these environments to prevent overweight/obesity and reduce plasma cholesterol to reduce risk of NCDs in the general population. Both dietary habits, overweight/obesity and cholesterol levels have been shown to track from childhood to adulthood. Establishing healthy dietary habits and weight status among children is thus important to prevent NCDs. To assess the overall impact of policies and societal changes on diets of children, we need to monitor what children are eating. The results from national dietary surveys are important for policy makers and white papers, and the Norwegian Directorate of Health needs this information to make action plans and dietary guidelines for the general population. The results from our national survey have been an important basis for the white paper "Nasjonal handlingsplan for bedre kosthold (2017-2021).". Moreover, the Directorate of health use the national survey data to promote health in the Norwegian population and make action plans for dietary habits in their yearly report "Utviklingen i norsk kosthold - Helsedirektoratet". The national survey data is also used by the Norwegian Scientific committee for Food and environment in their risk assessments. The results from the BRA-study have been taken forward by the Information bureau for fruit and vegetables in their "5 a day Kindergarten" scheme. Furthermore, in January 2017 a workshop to discuss food and meals in kindergarten was initiated by the project and jointly organised with the Norwegian Directorate of Health and Centre for food, health and physical activity. This was an important input for the revised guidelines for kindergartens published in December 2017 where the project is referred to under the recommendation about serving fruit and vegetables every day with a link to the material. The questionnaire for measuring guideline adherence was taken up by the public health project RØRE (Move) in the county of Østfold

in order to evaluate on of the aim of their projects. This led to a collaboration for the development and testing of the implementation intervention in the project. Thus, the project has influenced both the practice in Østfold county and the practice of the Norwegian Directorate of Health with regards to implementation of the guideline. Furthermore, these results can be directly transferable to implementation of other guidelines which the Norwegian Directorate of Health is responsible for and especially the ongoing work on a possible implementation of a free school meal. The impact of measuring cholesterol early in life is that it is the total cholesterol burden who define the risk of CVD. If we can detect children with high cholesterol early in life, lifestyle changes can be made in order to prevent CVD later in life. Our findings are in line with many European projects where initiatives have been initiated to start cholesterol screening among infants. We have discussed this in the national nutrition council and aim to suggest that a working group is started with the mandate of investigating the impact, feasibility, and economic benefit of initiating such a screening program in Norway. Several countries in Europe have already initiated a universal cholesterol screening program among children (Slovenia, Croatia, Luxembourg) or have started up large pilot studies (Germany and UK). Identifying children with high lipid levels and intervene with lifestyle counselling will favourably impact lifetime cardiovascular risk.

**5. Sources to corroborate the impact** (indicative maximum of ten references)

**1.** Data from the National surveys has been disseminated in the largest newspaper in Norway, Aftenposten [Barn drakk dobbelt så mye brus for 16 år siden (aftenposten.no),](#)
**2.** Data from the National surveys have also been used by the Norwegian Scientific Committee for Food and Environment in their risk benefit analysis of fish intake in the Norwegian population [Benefit and risk assessment of fish in the Norwegian diet (alsaker.no)](#)
**3.** Children and cholesterol measurements; Bør jobbe med kolesterolet allerede hos barn; Dagens Medisin, 2021**.** [Bør jobbe med kolesterolet allerede hos barn (dagensmedisin.no)](#)
**4.** Children and cholesterol measurements; was shown at the national news, 2022; [Professor Kirsten Holven mener alle barn bør få tilbud om kolesterolmåling – NRK Norge – Oversikt over nyheter fra ulike deler av landet](#)
**5.** Children and kindergartens and at home to increase intake of vegetables; interview with Nanna Lien at national radio 2014; [90 Vestfold-barnehager med på undersøkelse – NRK Vestfold og Telemark – Lokale nyheter, TV og radio](#)
**6.** Increase intake of vegetables among children**;** [Skal få barn til å spise mer grønt (forskning.no)](#)
**7.** Increase intake of vegetables among children; Deltar i et grønnsakprosjekt; interview with Anne Lene Kristiansen at national radio 2015**;** [Den som spiser gulrøtter ... – NRK Vestfold og Telemark – Lokale nyheter, TV og radio](#)
**8**. Increase intake of vegetables among children; interview with Nanna Lien in local newspaper. [Vil ha mer grønnsaker til barna (sandeavis.no)](#)
9. [Mat og måltider i barnehagen - Helsedirektoratet](#)

# [University of Oslo, Institute of Basic Medical Sciences] [case number 4]

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|---|
| Institution: University of Oslo, Faculty of Medicine |
| Administrative unit: Institute of Basic Medical Sciences, Department of Behavioural Medicine |
| Title of case study: Well-being among students and professionals |
| Period when the underpinning research was undertaken: 1993-2022 |
| Period when staff involved in the underpinning research were employed by the submitting institution: 1995-2022 |
| Period when the impact occurred: 2012-2022 |

1. **Summary of the impact** (indicative maximum 100 words)
The NORDOC and NORVET studies have yielded new knowledge that has informed interventions and preventive measures both in undergraduate and postgraduate training. The NORVET study has had a particularly large impact in the general media from 2020-22, and there has been increased awareness about work stress in trainees in medicine and veterinary medicine in Norway. Two important intervention schemes, an RCT of Mindfulness based stress reduction in medical and psychology students, and the Villa Sana intervention to reduce burnout in physicians, have proved effective in long-term follow-up studies, and these studies have had impact in both policymaking and health.

2. **Underpinning research** (indicative maximum 500 words)
*The nationwide NORDOC study* (The Longitudinal Study of Norwegian medical students and doctors) involves 1052 medical students in two cohorts, who were followed up in 7 waves during 25 years until 2019. This has resulted in about 50 original publications and altogether 10 PhDs. Five PhDs were awarded during the impact period: Grotmol 2012, Solberg 2017, Hertzberg 2018, Mahmood 2019, and Belfrage 2020. Major findings were a decline in work stress and severe depressive symptoms during the years of the career, with the exception that work home conflict is enduring and that this factor also predicts burnout from 10 to 15 years after medical school. Perceived skills in history taking and writing medical records are an independent predictor of perceived mastery of clinical work 20 years later. Low levels of neuroticism increased the risk of experiencing workplace violence from patients during 20 years follow-up. For NORDOC summary see: Facebook: @docsinrush
*The NORVET study* involves all 4000 Norwegian veterinarians approached in a postal survey in 2020 with a focus on mental health and individual and work-related factors, but in particular on serious suicidal thoughts and professional help seeking, using several similar measures to those in the preceding NORDOC. The NORVET study found a relatively high rate of suicidal ideation (20% thoughts and 5% serious suicidal thoughts) and reported work problems to be associated with such thoughts. Only half of those with perceived mental health treatment needs had sought help, and this applied even to those with serious suicidal thoughts.
Both NORDOC and NORVET had relatively high response rates, NORDOC, 60-80%, and NORVET, 75%. They are among the most representative studies ever in these professions, in particular with a relatively high rate of female participants.
The NORDOC studies has informed two interventions with long-term follow-up. These studies are also collaborations with other national institutions.
(1) *The Villa Sana study* is a follow-up of physicians seeking a counselling intervention for burnout at Modum Bad Hospital (N=227), and the Institute for Research of the Medical Profession (IRMP), Oslo. A major finding here was a reduction in burnout at 1 and 3 years follow-up, but also the importance of full time sick leave after the intervention as predictive.

(2) *An RCT of mindfulness training* in psychology and medical students (N=288) was a collaboration between the Department, The Institute of Health and Society at our Faculty, and the University of Tromsø. This study had long-term follow-ups, 4 and 6 years, and found that possible mechanisms for the effect of mindfulness training seem to be an increase in active problem focused coping and a reduction in avoidance coping.

- **Professor Reidar Tyssen** (2012-2022) leads the research team of Health Professions at the Department and has directed the NORDOC survey during the impact period. He received grants for the NORVET study for **PhD Helene Seljenes Dahlum** who was with our department (2019-2022). Other members: **Professor Erlend Hem** (2018-2022), p**rofessor emeriti Per Vaglum** (2012-2018), **Tore Gude** (2012-2020) and **Torbjørn Moum** (2012-2022). Dr **Karin Isaksson Rø, had her PhD** with us and affiliated member of the team.
-

3. **References to the research** (indicative maximum of six references) Authors in bold are in positions/associates at the Dept Behav Med/Institute of Basic Medical Sciences at the time of the research

**Isaksson Rø KE, Tyssen R, Gude T,** Aasland OG: Will sick leave after a counselling intervention prevent later burnout? A 3-year follow-up study of Norwegian doctors. *Scandinavian Journal of Public Health* 2012; 40:278-285

**Hertzberg TK, Rø KI, Røvik JO, Ekeberg Ø, Gude T, Moum T, Vaglum P, Tyssen R**. Work-home interface stress: and important predictor of emotional exhaustion 15 years into a medical career *Industrial Health* 2016; 54:139-58 (accept. online 2015)

De Vibe M, Solhaug I, Rosenvinge J, **Tyssen R**, Hanley A, Garland E. Six-year positive effects of mindfulness-based intervention on mindfulness, coping and well-being in medical and psychology students: results from a randomized controlled trial. *PLoS One*. 2018, 24;13(4):e0196053

**Nøland ST, Taipale H, Mahmood JI, Tyssen R**. Analysis of Career Stage, Gender, and Personality and Workplace Violence in a 20-Year Nationwide Cohort of Physicians in Norway. *JAMA Netw Open*. 2021 Jun 1;4(6):e2114749

**Dalum HS, Tyssen R, Hem E.** Prevalence and individual and work-related factors associated with suicidal thoughts and behaviours among veterinarians in Norway: a cross-sectional, nationwide survey-based study (the NORVET study). *BMJ Open*. 2022 Jan 3;12(1):e055827.

**Dalum HS, Tyssen R, Moum T, Thoresen M, Hem E.** Professional help-seeking behaviour for mental health problems among veterinarians in Norway: a nationwide, cross-sectional study (The NORVET study). *BMC Public Health*. 2022 Jul 7;22(1):1308. doi: 10.1186/s12889-022-13710-y.

4. **Details of the impact** (indicative maximum 750 words)
**Education and training in medicine and school**
Our team has made a major contribution to research in medical education. Tyssen (26 articles), Vaglum (25) and Gude (16) are the three most productive authors of such research in Norway. For instance, Belfrage et al found the importance of communication skills training in medical school. Perceived medical recording skills (including history taking) at the end of medical school predicted perceived mastery of clinical work 10 and 20 years later, also when controlled for personality and other factors.

Tyssen has also been at the editorial board on BMC Medical Education (Associate Editor) 2009-2018 and a member of the Research Committee in AMEE (Association of Medical Education Europe) 2014-2018.

In 2015, OECD invited Tyssen to the Expert Panel of the ongoing programme for upper secondary school, OECD Education 2030, much because of research on mindfulness training in students. In the panel and Focus group 2B, he emphasized the importance of flexibility and change in a VUCA world (Volatile-Uncertain-Complex-Ambiguous). "Transformative competencies" (creating new value, taking responsibility, and reconciling tensions and dilemmas) have become an important part of the Learning compass developed by this OECD programme.

**Physician personality and well-being**

NORDOC is one of very few projects in epidemiology that included a measurement of personality traits (BCI-36). NORDOC studies have shown the independent predictive validity of personality for mental health and work. Tyssen is the only Non-American author in a Springer textbook about Physician Mental Health and Well-being with a chapter on Personality traits. Tyssen was also the only European invited to the summit "Joy in Medicine" arranged by the American Medical Association in 2016. The burnout rate among physicians in the USA is high, but they lack longitudinal research such as NORDOC.

The Villa Sana programme runs week-long schemes for doctors and their partners with burnout, and our research team has been active in studying the effects of this programme (Isaksson Rø, Gude, Tyssen, Vaglum) in collaboration with the IRMP. The lectures at Villa Sana refer to many findings from the NORDOC studies, both with respect to the preventive importance of colleague support and balancing life, and in addition, the programme includes mindfulness training.

Both Isaksson Rø and Tyssen have given several plenary talks at national conferences for physicians, and they have given several interviews to the general media in the period. As such, they have had an important impact on the increased awareness about work and mental health among physicians in Norway. At the end of the impact period, there was an increased number of physicians seeking support at Villa Sana, particularly young female physicians.

Tyssen has given plenaries at several international conferences, the last two in 2019: a plenary at YES (Young European Scientists) in Porto and a keynote at the 21st Nordic Congress of General Practice, Aalborg, "Well-being for GPs and practice staff"

A NORDOC study published in JAMA Network Open (IF=13.8) in 2020 received much attention also in general media, news report in NRK P1, other newspapers, and a podcast with the Norwegian Medical Association ("Stetoskopet")

**Veterinarians' mental health and well-being**

There is a known increased risk of suicide among veterinarians, even higher than that among physicians in many countries. Dr. Dalum, who is a veterinarian herself, has been very active in the media and contributed to about 50 newspaper reports. Even before the start of her PhD project she gathered 350.000 NOK of grants for running expenses from veterinary organization and the industry. She headlined "Dagsrevyen" in NRK TV and a large report in Dagens Næringsliv, a recommended Norwegian newspaper.

The finding that one out of three Norwegian vets finds that life is not worth living was the second most read report on "forskning.no" from the University of Oslo in 2022. She has also contributed to several podcasts, among those in USA and Australia.

She and a colleague has started Psycho-Vets. They tour both in Norway and abroad to disseminate knowledge about prevention of burnout.

Another important impact is the implementation of mental health and communication skills training in the curriculum for veterinary students in Norway.

**5. Sources to corroborate the impact** (indicative maximum of ten references)

Medisinsk pedagogikk som forskningsfelt i Norge – en bibliometrisk studie.

Kvernenes M, Armitage CS, Almeland SK, Birkeli CN. Tidsskr Nor Laegeforen. 2023 Nov 28;143(18). doi: 10.4045/tidsskr.23.0398

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**Tyssen R**. Personality traits. In: KJ. B, MB. R, editors. Physician Mental Health and Well-being: Research and Practice. Integrating Psychiatry and Primary Care. USA: Springer; 2017. p. 211-34. https://link.springer.com/chapter/10.1007/978-3-319-55583-6_10

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Suicide among veterinarians – Headline Dagsrevyen NRK : Dagsrevyen 21 – 10. desember 2020 · Selvmord blant veterinærer – NRK TV

Mange veterinærer sliter med selvmordstanker - Institutt for medisinske basalfag (uio.no)

Flynn's Talk | Ep 23 - Psycho Vets; the NORVET Project | Flynn's Talk (podbean.com)

Fighting Burnout Across the Globe (galaxyvets.com)

Hverdagspsyken: Veterinærer og psykisk helse m/ Maria Tysnes, Reidar Tyssen & Helene Seljenes Dalum on Apple Podcasts

Veterinærer sliter med tanker om selvmord og at livet ikke er verdt å leve (khrono.no)

# [University of Oslo, Institute of Basic Medical Sciences] [case number 5]

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| **Institution: University of Oslo (UiO)** |
| **Administrative unit: Institute of Basic Medical Sciences (IMB)** |
| **Title of case study: Models for the management of the covid pandemics in Norway** |
| **Period when the underpinning research was undertaken: 2015-2022** |
| **Period when staff involved in the underpinning research were employed by the submitting institution: 2015-2022** |
| **Period when the impact occurred: 2020-2023** |

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**1. Summary of the impact**

OCBE's research has been essential for the management of the covid pandemic in Norway. From the very start of the pandemic, we have developed and run our mathematical and statistical models to (1) estimate the reproduction number R in each region of Norway, (2) to perform prediction of the number of hospitalised covid patients; and (3) to perform what-if studies on the efficacy of interventions (vaccines, lockdown and re-opening strategies …). Our results were regularly used by the National Institute of Public Health (NIPH), the Health Directorate, hospitals, national and local governments, to take key decisions. During the pandemic, OCBE and NIPH had a joint modelling team constantly on duty, also responsible for communication with the public (weekly reports) and the media. Norway's handing of the pandemic is recognised as very successful, and this is also thanks to our contribution.

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**2. Underpinning research**

**State-of-the-art by 2015:** *Stochastic compartmental metapopulation models* were known to be useful for situation awareness, forecasting and scenario simulation in epidemics. Informed by multiple sources of data (incidence of cases, hospital admissions), they allow to quantify the strength of viral transmission (reproduction number R), to estimate the number of infected individuals, and to predict the future number of infected and of hospitalized patients. *Individual-based models* were known as mathematical representation of an interacting population, with their demography and transmission networks in different social layers (households, schools, workplaces).

**Our contribution per 2019:** OCBE and NIPH, within our sfi BigInsight, had projects and PhD students in models for epidemics, which turned out to be essential for our Covid work:

R1. We developed a new spatio-temporal stochastic model for the spread of an infection based on mobile phone mobility and a sequential Approximate Bayesian Computation (ABC) for efficient inference. (2019 PhD Solveig Engebretsen, then started at Norsk Regnesentral (NR).)

R2. We developed an individual-based model, reproducing the Norwegian population's sociodemography, representing households, hospitals and nursing homes, calibrated to 2008–2015 and applied to MRSA bacteria. (2019 PhD Francesco Di Ruscio, started at NIPH.)

**Our contribution during the Covid pandemic 2020-2022:** Already in February 2020, OCBE, NIPH, NR and Telenor formed the Oslo Covid-modelling group. Throughout the pandemic, our relentless efforts, built on expertise and new scientific findings, allowed us to produce essential modelling results for Norway. Below, key methods developed during this period, which were in daily use and turned out to be powerful instruments for epidemic management for Norway:

- We extended R1 to Norway, using the Norwegian Telenor mobile phone mobility data (updated every six hours during the whole pandemics).
- Real-time inference was crucial, with data arriving on Monday mornings and results required by Wednesday mornings. Existing algorithms couldn't handle time-piecewise constant reproduction numbers (changing every 2-3 weeks). To address this, we created a novel

- sequential ABC, named split-seqABC, enabling efficient use of our stochastic metapopulation models with a high parameter count.
- Daily changing reproduction numbers are more precise than time-piecewise constant reproduction numbers. We developed a new model with daily-varying reproduction number, to quantify the viral transmission in real time. We proposed a state-space formalisation of the model and a sequential Monte Carlo approach which also runs in real-time.
- Throughout the COVID years, we routinely received specific inquiries from the government and others, involving decisions on optimal interventions. To address these what-if scenarios, we enhanced our individual-based model R2, dividing Norway into 13,521 cells, each with the actual population. The model incorporated various age-structured contact routes, such as community, household, school, and workplace, utilizing Telenor mobility data. This refined model proved instrumental in guiding decisions, including optimizing vaccination strategies and post-Omicron lockdown reopening. It stands as the most advanced individual-based model for Norway, surpassing the level of detail found in comparable models, such as the UK ones.
- In addition, we produced results on specific aspects of covid epidemiology, which had impact on the management of the pandemics. For example:
  - We compared Omicron's epidemic growth to Delta's, using December 2021 - January 2022 contact tracing data. We found increased Omicron susceptibility despite three-dose vaccination, with infected individuals efficiently spreading the virus, while three-dose vaccinated contacts had lower infection risk.
  - We criticised for major shortcomings in design and methodology, a randomised trial on Covid transmission in fitness centres in Oslo, suggesting that these were not a place of special spread.
  - We established an international multidisciplinary research group to develop a questionnaire for patients with or after covid disease, including long-covid, to assess their health-related quality of life. The questionnaire has been used in many clinical studies, and for example help to conclude that Baricitinib should not be used to treat Covid patients.

**Our contribution after the Covid pandemic:** We continue publishing our methods and findings, to document our work and to prepare for future pandemics. For example, our analysis revealed that mandating recommendations to reduce contacts did not result in fewer contacts compared to just recommendations. Consequently, less intrusive and costly non-mandatory measures may prove effective in Norway in the future.

**Funding:** BigInsight, NFR, Nordforsk; In-kind: UiO, NIPH, Telenor, NR; Supercomputing: UiO, Sigma2.

- Oslo Covid-modelling group, included:
- Birgitte Freiesleben de Blasio – NIPH and OCBE (20%) (leader)
- Arnoldo Frigessi – OCBE (leader)
- Francesco Di Ruscio – OCBE (PhD) and NIPH
- Solveig Engebretsen – OCBE (PhD) and NR.
- Chi Zhang – OCBE (PhD) and NIPH.
- David Swanson (OCBE)

- Contributors from OCBE in additional activities:
Jon Michael Gran, Marissa Erin LeBlanc, Morten Valberg, Corina Silvia Rueegg, Ragnhild Sørum Falk

**3. References to the research**

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Di Ruscio, F., Guzzetta, G., Bjørnholt, J.V., Leegaard, T.M., Merler, S. and De Blasio, B.F., 2019. Quantifying the transmission dynamics of MRSA in the community and healthcare settings in a low-prevalence country. *Proceedings of the National Academy of Sciences*, 116(29), pp.14599-605.

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Kamineni, M., Engø-Monsen, K., Midtbø, J.E., Forland, F., de Blasio, B.F., Frigessi, A. and Engebretsen, S., 2023. Effects of non-compulsory and mandatory COVID-19 interventions on travel distance and time away from home, Norway, 2021. *Eurosurveillance*, *28*(17), p.2200382.

Günther, F., Brustad, H.K., Frigessi, A. and Britton, T., 2024. Quantifying the impact of social activities on SARS-CoV-2 transmission using Google mobility reports. Submitted to PNAS, available on *medRxiv*.

Valberg, M., Gran, J. M., Rueegg, C. S., & LeBlanc, M. (2022). Letter to the editor regarding "Covid-19 transmission in fitness centers in Norway-a randomized trial". *BMC public health*, *22*(1), 1-2.

## 4. Details of the impact

OCBE was a founder and key part of the Oslo Covid-modelling group: key scientific results originated from OCBE, De Blasio and Frigessi were joint leaders of the group, with their ex-PhD students fully active. The impact was during the whole pandemic (2020-2022) and continues today in terms of preparedness for future pandemics. We were part of the NIPH pandemic management during the whole period, with responsibility for all modelling and predictions. The groups included about 15 researchers, including system and data engineers and epidemiologists, in addition to us statisticians. We were responsible for all methodology and algorithms, including weekly runs. Typically, our week started Monday at 8 am, when we froze the current data and started running our models, with results ready on Wednesday morning, when the report was prepared and submitted at 12:00. The modelling group had a meeting on Monday at 8:00 to decide what algorithms to run, on Wednesday to discuss results and on Friday to critically discuss and decide about needed improvements and planning the specialised reports, with hard work all week long, often including weekends: week after week, taking turns during vacations. In addition, we were responsible for communication with the public and media on all modelling and prediction. Meetings were also organised with health authorities that used our results and regularly with all the Nordic health authorities.

Our results reached immediately the health authorities and the government. The R-number was used in the public discourse, including uncertainties in estimating it. We experienced several times to hear the minister or the health directors to cite from our reports during press conferences on tv, just few hours after publication.

It is difficult to quantify the impact of our results. We dare to say that the beneficiaries is the whole Norwegian population, in terms of lives saved, reduced hospitalisation and illness, increased economical benefits. Norway as a country, has been able to manage the pandemics well, citing from the national Coronavirus Commission: "The country's population and its authorities have

handled the pandemic well overall. Norway has had one of Europe's lowest mortality rates, least restrictive infection control regimes and smallest declines in economic activity." One reason for this is the timeliness with which the national and the local governments have introduced interventions, to prevent the spread to explode. Our estimates and predictions were making this possible.

In order to give evidence of the importance of our work, we cite (our translations) from the report of the Coronavirus Commission, "Evaluering av pandemihåndteringen - Rapport fra Koronautvalget, 29. april 2022, for å gjennomgå og trekke lærdom fra koronapandemien i Norge", see section 12.3.5 on "Matematisk infeksjonsmodellering": "The situational understanding included mathematical modelling to estimate the disease burden of the epidemic in the coming weeks. Mathematical infection modelling was part of a comprehensive knowledge base, and NIPH's professional advice was always provided based on a holistic assessment. - By quantifying health loss and the burden of measures, the [modelling] group could highlight the societal consequences of reducing imported infections, differentiating measures geographically, or illustrating how characteristics of the virus variant influenced the choice of strategy. - Throughout the pandemic, projections of infection numbers, hospitalizations, and sick leave were crucial parts of the government's decision-making basis. The committee believes that such projections have clear utility as decision-making tools and should, therefore, be used in future crises."

The report in section 12.3.5 also includes two statements, here translated: Prime Minister Støre described his relationship with the models and that these results were useful in "challenging decision-makers to consider what to do with hospital capacity … that must be scaled up if [the predictions would] materialize." Espen Nakstad, Assistant Director of the Norwegian Directorate of Health, said on the role of models and predictions: "It has probably influenced political decision-makers, both locally and nationally, especially to see alarming models. It is important to say. But we have contributed to seeing it not as forecasts but possible scenarios. In that sense, I don't think it has always been very decisive."

In addition, we believe that a further impact of our work, of more long term and educational type, is the increased understanding by the general population of uncertainty quantification of predictions. We think that recognising the presence of uncertainty in decision making, can more generally help to increase the trust in government and politics – important in our current world.

OCBE also participated (with JM Gran) to the national commission responsible for deciding whether to stop the use of the Astra-Zeneca vaccine.

Mistakes we did in the covid period also made an impact, not only our correct results: we failed to explain well enough the assumptions of our three-week ahead predictions. These were such that we predicted the number of new covid hospitalisations, given that no new intervention would be implemented, and given that the population would continue to have the same mobility. Aftenposten, the main Norwegian newspaper, found that our predictions were pessimistic when the spread was increasing, and this was the main news on 15 June 2021. The reason for this difference was that when our predictions were alarming, then governments often would introduce additional restrictions and people would naturally behave more carefully, thus leading to less hospitalisations than predicted. We tried to explain this, but it was difficult.

Finally, we mention possible long term impacts of our work: We are preparing scientific papers which use the Norwegian and Nordic data to explain if and how interventions were useful, with the hope to increase knowledge for future situations. We mention that while NIPH had to cut their staff significantly, their modelling team was not reduced, recognising the importance of our work.

**5. Sources to corroborate the impact**
Weekly reports *Situational awareness and forecasting for Norway,* published from 14.4.2020 until 25 may 2023 (Tidligere publiserte rapporter):
https://www.fhi.no/ss/korona/koronavirus/koronavirus-modellering/
An example is here, for 24 November 2022:

https://www.fhi.no/contentassets/e6b5660fc35740c8bb2a32bfe0cc45d1/vedlegg/nasjonale-og-regionale-rapporter/2022-11-24-national_regional_model_22.pdf

The NIPH published also a weekly report which always included a summary of our results, which then were seen in a global perspective ("Alle ukerapporter 2020-2023", in Norwegian) https://www.fhi.no/publ/statusrapporter/luftveisinfeksjoner/#alle-ukerapporter-2020-2023

Example of report prepared to answer a specific question of the government, here on the possible vaccination of children between 12 and 15 years (in Norwegian), 26 August 2021: https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021-09-02-oppdrag-45_vedlegg-2_modelleringsrapport_rettet.pdf

Example of report where modelling was a major component: Socio-economic assessment, 15 February 2021, see for example tables V.1 and V.7, among many results from our models: https://www.fhi.no/contentassets/3596efb4a1064c9f9c7c9e3f68ec481f/2021-09-02-oppdrag-45_vedlegg-2_modelleringsrapport_rettet.pdf

Example of impact of our quality-of-life questionnaire, to stop using a certain treatment: https://www.helsedirektoratet.no/veiledere/koronavirus/vaksiner-smittevernutstyr-og-legemidler/legemiddelbehandling-behandling-av-covid-19/bruk-av-baricitinib-olumiant

Selection from the media (in Norwegian):
- Into the Unknown, Klassekampen, 17 March 2020: https://klassekampen.no/utgave/2020-03-17/inn-i-det-ukjente
- The FHI expert does not think we will get the R-number below 1 again, NRK, 24 march 2021, https://www.nrk.no/norge/fhi-ekspert-tror-ikke-vi-far-r-tallet-under-1-igjen-1.15431839
- Aftenposten makes mistakes on forecasts. Again and again. Aftenposten, 18 June 2021, https://www.aftenposten.no/meninger/kronikk/i/7KbAKo/aftenposten-bommer-om-prognoser-igjen-og-igjen, answer to the article on Aftenposten of 15 June 2021: https://www.aftenposten.no/norge/i/0KLBLG/prognosene-bommet-fullstendig-paa-antallet-pasienter-igjen-og-igjen
  Posted on social media (17.000 impressions; Frigessi had 1500 followers during the pandemics) https://x.com/freeges/status/1472596466686386186?s=43
- More recently: Mandates during the pandemic had a greater effect in large cities, Finansavisen, 1 may 2023, https://www.finansavisen.no/samfunn/2023/05/01/8004900/pabud-under-pandemien-hadde-storre-effekt-i-store-byer?zephr_sso_ott=Oq3Qk7
- In English: COVID-19: The Norwegian model, The UNESCO Courier, 15 December 2022, https://courier.unesco.org/en/articles/covid-19-norwegian-model

During the pandemic, we gave many ZOOM presentations, including for example:
- Alan Turing Institute, London, 17 March 2022: https://www.turing.ac.uk/people/guest-speakers/arnoldo-frigessi
  https://www.turing.ac.uk/events/probabilistic-approach-situation-awareness-and-forecasting-covid-19-pandemics-norway
- Data Science in the Post-Covid World, University of Helsinki, 11 May 2021 https://www.helsinki.fi/en/faculty-science/news/hidata-webinar-data-science-post-covid-world-11-may-2021

"Evaluering av pandemihåndteringen - Rapport fra Koronautvalget, oppnevnt ved kongelig resolusjon 29. april 2022 for å gjennomgå og trekke lærdom fra koronapandemien i Norge" https://www.regjeringen.no/contentassets/b1dace9390054c85a5a87c7bbf1bc384/no/pdfs/nou202320230016000dddpdfs.pdf

Camilla Stoltenberg, director of NIPH, thanks BigInsight for the work during Covid times, in Norwegian, subtitled; her video is the first linked in this page: https://www.biginsight.no/news/2023/11/21/biginsight-celebration-day-was-fun