NEAR: The National E-infrastructure for Aging Research in Sweden. Strategic plan

PRIMARY PURPOSE AND INCLUDED DATABASES

The primary purpose of our initiative is to build and run a *National E-infrastructure for Aging Research* (NEAR; http://near-aging.se/) by integrating the existing databases from 15 major population-based studies on health in aging in Sweden, thus facilitating aging research in Sweden, fostering international collaboration, and enhancing the quality of research and generalizability of research findings. Ultimately, by empowering aging research in Sweden, NEAR will contribute to identifying sustainable intervention strategies that will help us achieve better health and care for older people.

Why an infrastructure on aging research? The demographic transition toward an older population in the past half century poses tremendous long-term societal challenges in Sweden and globally. Sweden has one of the highest proportions of older people in the world: about one-fifth of our population is 65 years or older, and the oldest-old (age 85+) are the fastest growing segment of the population. Although we now live longer and healthier lives, the aging of the population is leading to an increasing number of people with chronic disorders and functional dependence, which greatly impacts families and societies. Understanding how social, biomedical, and behavioral factors relate to later-life health conditions is of utmost relevance when we aim to compress disability and morbidity into a short period toward the end of life. Such compression is crucial not only for individuals but also to reduce the economic and societal burden of late-life disability and morbidity.

Beginning as early as the 1970s, several population-based studies on health and aging were implemented in Sweden. Indeed, Sweden has a long tradition of community-based studies on aging and mental health and is one of the leaders in the research field of dementia and other mental disorders in older people worldwide. Sweden's high level of competence in social gerontology, geriatric epidemiology, public health, and other aging-related disciplines, together with the availability of numerous population-based studies, provides the ideal basis for establishing a national infrastructure like NEAR.

Databases included in NEAR (http://near-aging.se/Databases.html).

At the moment, NEAR consists of 15 databases, including three databases already supported by VR as national infrastructures (Table 1). All databases share the following characteristics:

- Data are derived from population-based longitudinal projects, well known nationally and internationally, which include more than 170,000 people over age 50;
- Participants are older adults who have been assessed by direct interview or/and clinical examination and followed up a minimum of seven years to a maximum of 40 years;
- All projects have received ethical approval at each phase of assessment as described in detail in the attachment on ethical considerations;
- The extraordinary number of studies (more than 500) derived from the databases have already generated relevant knowledge on health and health care in aging.

NEAR will be a **dynamic infrastructure** for the following reasons:

- It is based on ongoing exchanges with the local databases and with the external users;
- It will be constantly developed, as it is designed to be project-driven; and
- It will be enriched in the future by a) collection of new data_in the ongoing included projects, b) incorporation of more datasets from other longitudinal studies, and c) linkage with registers such as clinical quality registers (SveDem, SeniorAlert), hospital-based registers (GEDOC), or national registers (the Swedish Prescribed Drug Register).

Table 1. Databases from the 15 population-based longitudinal studies included in NEAR $\,$

PI	Description
L Nyberg Umeå University	Betula Project (http://www.org.umu.se/betula/) aims to trace memory changes during adult life and old age (30+ years) and identify risk factors for cognitive decline and early preclinical signs of dementia. It started in 1988 with participants from Umeå, northern Sweden, who were examined every 5 years on 6 occasions [1]. N=4445 ; follow-up=30 years
G Malmberg Umeå University	Survey of Health, Ageing and Retirement in Europe-Sweden (SHARE) (www.share-project.org) aims to analyze the interplay between economic, health, and social factors in shaping older people's living conditions and health. Longitudinal surveys of 110,000 people aged 50+ from 21 European countries [2]. In Sweden, it included 3053 people followed up for 12 years.
L Fratiglioni Karolinska Institutet	Kungsholmen Project (KP) (www.kungsholmenproject.se) focused on the development and social consequences of dementing disorders. All registered inhabitants aged 75+ in Kungsholmen, Stockholm, were examined at baseline (1987-1989) and re-examined every 3 years until 2000 [3]. N=1810; follow-up=13 years
L Fratiglioni & A Wimo Karolinska Institutet	Swedish National study on Aging and Care in Kungsholmen (SNAC-K) (www.snac-k.se) & Swedish National study on Aging and Care in Nordanstig (SNAC-N) (www.snacnordanstig.se). Kungsholmen and Nordanstig are two of the 4 centers included in a national project to improve health and care of adults 60+ years. They started 2001-2004 with medical, psychological, and social assessment of the participants who were followed with same protocol every 3-6 years [4]. N=~4500 and 766; follow-up=16 years
Lennartsson & J Fritzell Karolinska Institutet	Swedish Panel Study of Living Conditions of the Oldest Old (SWEOLD) (www.sweold.se/start.htm) aims to investigate the impact of early and midlife factors on late-life health. Surveys on national samples in 1992, 2002, 2004, 2011, and 2014 included a variety of living conditions and health indicators. Linkage with the Swedish Level of Living Survey provides over 45 years of longitudinal data [5]. N=~3700; follow-up=over 40 years
NL Pedersen Karolinska Institutet	Screening Across the Lifespan of Twins (SALT) (http://ki.se/en/research/the-swedish-twin-registry) & Swedish Adoption /Twin Study of Aging (SATSA) (www.maelstrom-research.org/mica/study/satsa). Both aim to study the origins of individual differences in aging, including environmental and genetic factors. SALT includes ~45,000 twins aged 40+ identified via the Swedish Twin Registry, screened 1998-2002 and followed up in 2005-2008. SATSA includes 2018 twins aged 50+ followed every 3 years since 1984 [6].
A Wolk Karolinska Institutet	Swedish Mammography Cohort study (SMC) (http://ki.se/en/imm/unit-of-nutritional-epidemiology): a female cohort aged 40+ (n=~61,400) started in 1987 in central Sweden and followed in 1997 & 2008. Cohort of Swedish Men study (COSM): a male cohort aged 55+ (~50000) started in 1997 in central Sweden and followed in 2008. SMC and COSM aim to study the association between lifestyle, genetic factors, morbidity, and mortality in middle-aged and elderly people [7].
B Johansson Gothenburg University	Origins of variance in the Old-Old (OCTO-Twin) (http://ki.se/en/meb/octo-twin) aims to explore genetic and environmental bases of heterogeneity in the oldest-old. 351 twin pairs aged 79-98 from the Swedish Twin Registry, were clinically assessed on 5 occasions at 2-year intervals from 1991-1994 to 1999-2002 [8]. Follow-up=10 years
I Skoog Gothenburg University	Gothenburg Population Studies (http://agecap.gu.se/english/research) aim to explore interplay between genetic, biological, and psychosocial factors and their influence on mental health in old age. The cohorts are representative of older populations from young-old to oldest-old (H70, H85, H95+) in Gothenburg [9]. N=~2400; follow-up=40+ years
AD Aslan Jönköping University	Gender Differences in Health Behaviour and Health among Elderly (GENDER) (www.maelstrom-research.org/mica/study/gender) aims to study the origins of individual differences of unlike-sex twin pairs in the aging process. 249 unlike-sex twin pairs born in 1906-1925 in Sweden were evaluated in 1995-1997, followed by two additional in-person waves at 4-year intervals [10].
J Berglund Blekinge I. Technology	Swedish National study on Aging and Care in Blekinge (SNAC-B) (http://ltblekinge.se/snac). Blekinge is one of the 4 centers included in the national SNAC project started 2001-2004 in southern Sweden [4]. N=1402; follow-up=16 years
S Elmståhl Lund University	Swedish National study on Aging and Care in Skåne (SNAC-S) (www.med.lu.se/klinvetmalmo/geriatrik/gott_aaldrande_i_skaane). Skåne is one of the 4 centers included in SNAC. SNAC-S started 2001-2004 in southern Sweden [4]. N=2391; follow-up=16 years

AGING RESEARCH: STATUS OF THE FIELD AND FUTURE CHALLENGES

Aging is a life-long process of progressive changes. The functional capacity of biological system peaks in early adulthood and then progressively declines, but strong evidence indicates that health and functioning status in older people are largely determined by lifelong exposures and actions. Decades of research, including studies using the NEAR databases (Table 2), have led to three major contributions that also represent the **three major challenges** of the field in the coming decades. With NEAR, we can address these challenges with high-quality data of unique depth and breadth.

Table 2. Major scientific contributions from the participating databases

- Betula Project: This longitudinal project revealed a markedly later onset of age-related memory change than that suggested by cross-sectional data. It also demonstrated great heterogeneity in memory-aging profiles and linked such variability to genetic, lifestyle, and brain characteristics [1, 11].
- Gothenburg Population Studies (H70, H85 and H95+): These studies provided pioneering evidence linking vascular risk factors to vascular dementia and Alzheimer's disease. A further novel contribution is a better understanding of the role of midlife factors (obesity, hypertension, and high cholesterol) in late-life health conditions such as stroke, dementia, and depression [9, 12.
- *Kungsholmen Project*: This project uncovered the relevance of psychosocial factors in dementia, showing that a socially, physically, and mentally active lifestyle together with low vascular burden partly counteracts the genetic risk for dementia. These factors prolonged life by 5 years in people aged 75+ and protected people from multimorbidity and disability [3, 13].
- *OCTO-Twin Study*: This project has shown the relevance of preserved cognitive function for survival, well-being, and physical capacity in the old-old (age 80+). Although the effect of genetic background is strong, even identical twins age differently [14].
- *SALT*: The project is one of the few in the world that could quantify the genetic and environmental influences in (1) common chronic disorders of older people and (2) individual changes in physical and cognitive functioning through the lifespan. SALT also made pioneering contributions on the relevance of diabetes and inflammation in neurodegeneration [15].
- SATSA: Data from this dataset have greatly contributed to our understanding of how genetic and environmental factors work together to influence physical and mental health [16].
- SHARE-Sweden: This project has explored the consequences of different welfare regimes on aging, the role of informal and formal care across Europe, feelings of loneliness in different European regions, and impact of physical activities on depression in older people [2].
- *SMC and COSM*: The greatest contributions of COSM and SMC have been in the field of nutrition and cancer, especially breast and prostate cancer. As the cohorts aged, we are able to investigate physical activity and diet in relation to health and survival of older people [7, 17].
- SNAC: SNAC-K showed that dementia incidence and disability have declined in the last 2 decades. SNAC-B revealed the importance of dental health in older people and its relationship with cognition. SNAC-S showed the need for different cut-offs in several biological tests in 70+ old people. The estimated costs of formal and informal care of people with dementia from SNAC-N have been used by WHO and the Swedish National Board of Health and Welfare. Finally, several studies from SNAC-K and SNAC-N have shown the extent of inappropriate drug use and inequalities in drug treatment related to socioeconomic status in older adults [18, 19].
- SWEOLD: Studies with SWEOLD have shed light on (1) the relevance of living conditions and family connections to well-being and healthy aging and (2) health inequality in older people by gender, education, and socioeconomic position in Sweden. Research on health trends and midlife determinants has underlined the need for using multiple health indictors and a life-course approach [5, 20].

Challenge 1: Health in aging is a complex, multidimensional, dynamic process.

Developing a disease may greatly affect health of older people, but measures of morbidity alone are insufficient to capture the complexity of health; functioning must also be taken into account. Rather than absence of diseases, health is a state of social, physical, and psychological well-being that allows people to live actively in accordance with their needs and preferences. However, our current knowledge about health in aging concerns only single dimensions of health and interpersonal differences confound our understanding of intrapersonal changes. Little is known about variations in individual health. Health trajectories can significantly complement the conventional measures of health outcomes by providing information related to how health evolves over time. *NEAR has the potential to fill this gap*.

Challenge 2: Multidomain determinants of health in aging. Poor health is not a necessary consequence of surviving to older age. A number of contextual, biographical, and biological drivers lead to important variations in older people's health trajectories, such as exercise, nutrition, social engagement and support, stress levels, occupation experiences, and allostatic mediators. Strong evidence supports the hypothesis that single or aggregated determinants from biomedical, environmental (social and physical) and psychological domains impact health in old age, but we still lack evidence on the interplay among the domains. NEAR provides a unique opportunity to explore health of the older people in relation to various determinants, their interaction and changes with time.

Challenge 3: Lifelong experiences and trajectories. We have ample evidence that as we age, our health status and risks for diseases are the outcomes of different life events starting at gestation and involving other life periods such childhood, adolescence, and adulthood. The life course approach has become mainstream in social sciences and epidemiology, but robust knowledge on the interrelationships between social and biological factors over the life course is still largely wanting. *NEAR has the potential to provide major contributions to this topic.*

NEAR: NATIONAL INTEREST AND ADDED VALUE

NEAR fulfills the 6 criteria established by VR to define an infrastructure of national interest:

- Be of broad national interest. Sweden has one of the oldest populations in the world, which underscores the urgent need for investing in aging research. NEAR will focus on aging, health, and care to identify intervention strategies for living longer and healthier lives.
- Provide conditions for world-leading aging research. A multidisciplinary perspective is needed in aging research. By harmonizing 15 datasets from medical and social fields, NEAR will include information on social gerontology, public health, biomedicine, and care science. The availability of multidisciplinary data in such a large population makes NEAR unique.
- Be exploited by several research teams or by users involved in high-quality research projects. Our current experience from the individual databases suggests that NEAR will be used by national and international researchers, health care professionals, government agencies, the industrial sector, and international organizations, as the infrastructure can provide unique information for aging research, policy and development, and innovation.
- Be of a large sample size and national coverage of older populations that make it impossible for individual research teams to manage. NEAR includes older populations from almost all parts of Sweden. The large sample size allows carrying out subgroup analyses, provides nationally representative data, and supports methods development.
- Be subject to a long-term plan. Long-term planning includes continuous expansion by adding new data collected in the individual databases, including additional databases, linking NEAR with various registers, and interacting with related international

infrastructures. We will be able to trace societal changes, time trends, and generational differences in health conditions in older population.

• Be open and easily accessible to researchers, industry, and other users, and be subject to an accessibility plan. It is in our interest to make NEAR available to researchers and other users once the infrastructure is established and we will develop detailed policy regarding accessibility, rules, and procedures for using NEAR. We aim to find solutions to facilitate and guarantee open access for all users while taking the ethical and legal aspects of sensitive personal data into account.

Added value

- The infrastructure will allow researchers from multiple disciplines, including social gerontology, biomedicine, public health, epidemiology, psychology, health economics, and care science to study a broad range of issues related to health in aging. This broad range of data cannot otherwise be provided by any of the individual databases.
- NEAR will promote not only data sharing, but most importantly, the sharing of different competences from medical, psychological, and social fields. This will be crucial to developing a new generation of highly and uniquely qualified researchers and to creating multidisciplinary networks.
- Specific research questions (e.g., on the societal burden and time trends of diseases, health determinants, and health care-related issues) can be addressed in nationally representative samples, and the generalizability of findings will be greatly improved.
- The inclusion of databases such as SHARE provides the opportunity to compare findings in European countries with different institutional and socio-cultural contexts.
- NEAR will benefit aging research by substantially increasing sample size and statistical power. Sample size and power are major limitations of most studies on individual-based care or gene-environment interactions for various health outcomes in old age.
- Along with the increased power, NEAR's nationwide coverage will allow researchers to capture the diversity of health in older adults in Sweden with regard to gender, education, socioeconomic position, living areas, living conditions, and earlier life events.
- Access to multidisciplinary data will make the field of aging research more attractive not only to researchers already working in the field, but also to clinical and basic scientists. In Sweden, only a limited number of basic scientists now work in aging research.
- NEAR will strengthen individual research groups' ability to find international collaborators and to recruit students and researchers from abroad.
- By ensuring the future development of aging research in Sweden and providing a critical mass of data, NEAR will further consolidate Sweden's leading international position in the research area of aging, health, and care.

SCIENTIFIC OBJECTIVES AND PLANNED PROJECTS

Our **vision** is that NEAR will provide important contributions to our understanding of social, biomedical, and psychological aspects of the aging process in relation to people's social and physical contexts across the entire lifespan. We can achieve this goal by coordinating the existing research on aging, health, and social care at the national level; integrating the databases already available in the various geographic areas and disciplines; and facilitating the use of such integrated, multidisciplinary information through the improved access provided by the new national infrastructure NEAR.

Scientific objectives. At least 5 scientific objectives can be achieved in NEAR's first 8 years:

1. Provide high-quality database resources for investigating determinants, pathways, and underlying biological mechanisms of common diseases (e.g., cardiovascular disease,

stroke, and dementia) and health conditions (e.g., multimorbidity, frailty, cognitive decline, and functional dependence) in older people;

- 2. Provide high-quality database resources for investigating public health-related issues in aging, such as national burdens and time trends of common diseases and health conditions;
- 3. Provide data for assessing and planning health care for older people by encouraging linkage to other registries;
- 4. Provide scientific evidence to design intervention strategies to improve health, medical, and social care and quality of life for older people; and
- 5. Provide reliable data for addressing issues of social inequality in aging and health.

Five research projects

In line with the five objectives, we have identified five research projects for which NEAR can provide the necessary data starting in year 3:

Project I: Exploring health trajectories in aging to better identify people at higher risk of severe negative outcomes and care services utilization. To achieve not only longer but also healthier lives, we need to assess individuals' health holistically going beyond the simple absence of diseases and trace their trajectories of health and functioning. NEAR will give us the opportunity to (1) include clinical diagnoses, physical and cognitive dysfunction, and disability and (2) monitor health changes at the individual level. Deterioration in older people's health may follow different trajectories from first biological changes to disease onset, functional loss, disability, and ultimately, death. The integration of several datasets will give us the opportunity to identify new pathways to healthier lives in old age.

Project II: The complex interrelationship between psychiatric and neurodegenerative disorders in older adults. Neuropsychiatric disorders are common in older adults, yet their effects on aging-related disorders are not well understood. Both sleep disturbance and depression could be risk factors for or early symptoms of cognitive decline and dementia or may interact with genetic factors (e.g., APOE) to prompt clinical expression of neurodegenerative disorders. NEAR will provide rich information on sleep and depression along with repeated measures of cognition and rigorous diagnosis of dementia over a long follow-up period. The enhanced power of the combined datasets will give us the ability to investigate how depression and sleep disturbances are related to dementia subtypes (even less common ones), and whether these psychiatric conditions are potential surrogate markers for preclinical stages of neurodegenerative diseases.

Project III: Not only in the genes. Gene-environment interplay explains why older adults age differently. Healthy behaviors and stimulating lifestyles may counteract the deleterious effects of genetic susceptibility and aging-related brain lesions. People with high brain reserve due to lifelong exposure to several protective factors have lower risk of cognitive decline and dementia than those with lower brain reserve despite similar levels of vascular and amyloid burden. Similarly, genetic vulnerabilities interact with a variety of environmental exposures to contribute to individual differences in aging. With NEAR, we can (1) explore how physical and mental health is affected by the interplay of genes and environment, (2) identify genetic vulnerabilities whose detrimental effects are preventable when combined with a particular environmental exposure, and (3) identify those who may potentially benefit from intervention.

Project IV: Identification of neuroimaging biomarkers in brain aging. The brain-maintenance theory states that relative lack of brain pathology is the primary determinant of successful memory aging. Brain maintenance can be measured at different "levels," including the integrity of brain grey and white matter with magnetic resonance imaging (MRI). Several databases in NEAR include detailed measures of memory and MRI, which offers a unique opportunity to test key predictors of the brain-maintenance theory and many other questions

on the relationship between brain integrity and cognitive function. The increased power provided by NEAR enables us to explore the role of genes and lifestyles.

Project V: Life course dynamics leading to social inequalities in health at old age. Inequalities in health between older people of different socioeconomic position (e.g., education, occupation, and income) are large and often grow over time. Differences in disability-free life expectancy are even larger than differences in life expectancy. Although such disparities are found in almost all countries, an intriguing question is the extent to which welfare policies influence these differences. Thanks to the inclusion of SHARE in NEAR, we will be able to carry out cross-cultural studies on older adults in Europe, relating health conditions to socioeconomic status and welfare policies. Finally, NEAR will not only examine how events and social circumstances over the life course are interrelated and lead to health inequalities in old age, but also specifically focus on social-biological transitions.

POTENTIAL USERS

We will develop full policies for sharing NEAR data with internal and external users while taking into account not only quality of the proposals but also ethical and legal issues due to the presence of sensitive personal data in our datasets (see attachment "NEAR: Description and Operationalization"). NEAR will be a unique data resource for numerous academic and non-academic users from Sweden and abroad. We expect the following users:

- *National users*. NEAR can be used by researchers to investigate medical and social issues related to aging, by students for their master's and PhD projects, by industrial actors for designing and developing medical and health care devices, and by health and social care organizations for planning and improving care services.
- International users. In Europe, NEAR can be a useful resource for graduate programs such as the summer school on epidemiological methods organized annually by Harvard University and KI. Furthermore, several participating datasets are already included in international multicenter studies or consortia (see "NEAR: Description and Operationalization"). NEAR will further support and facilitate these international exchanges. Finally, researchers and health professionals from North America and the Asia-Pacific region (Japan, China, and Australia) have already expressed interest in Swedish aging data for cross-cultural comparisons.
- Government agencies. National data are critically important for assessing and monitoring the health and care needs of the older population. NEAR can be used to guide resource allocation, plan the organization of health care, develop public health policies, and optimize health care and social services.
- *International organizations*. International professional organizations such as WHO, the World Stroke Organization, and Alzheimer's Disease International will also be interested in using NEAR to help develop global policies and guidelines.
- *Industry and other private organizations*. Several actors in the private sector, both non-profit organizations and businesses, are becoming increasingly interested in aging. The information available in NEAR will help them develop new services (social innovation) and products that can help older people achieve healthier lives.

Expected number of users and their research fields

It is difficult to estimate an exact number of future users of NEAR. On the basis of the current situation, we anticipate that researchers from multiple research fields will take advantage of the infrastructure: public health and epidemiology, gerontology, geriatric medicine, social science, psychology, care science, neuroscience, and genetics. One way to estimate the number of potential users is via the use of the databases included in NEAR. They are currently used by various groups for research, education, and policy development and by

international partners as part of national and international consortia. The databases are involved in over 20 international consortia, and used by ~100 academic institutions, and ~20 non-academic institutions.

RELEVANCE IN THE SHORT AND LONG TERM

Scientific relevance. The outstanding scientific track records of the participating PIs guarantee that the new infrastructure will be of high scientific caliber. Their diverse backgrounds provide the multidisciplinary perspective needed to ensure integrated research and high-impact findings. From a public health perspective, NEAR will contribute to identifying strategies to delay the onset of chronic conditions (e.g., multimorbidity, dementia, and disability) and mitigate their consequences. It has the potential to identify biological markers for early detection of diseases common among older adults, which can lead to early intervention and effective treatments. From a clinical point of view, research using NEAR will provide evidence to improve current guidelines for clinical practice. From a social care perspective, research derived from NEAR will facilitate the development of person-centered care and the integration of medical and social care services.

Significance for the scientific field in the long term. The scientific relevance of NEAR will increase as data from new follow-ups of the participating cohorts as well as new cohorts are added. Also, data harmonization will enhance the quality, accessibility, and usefulness of the data, which will lead to new research avenues, new analytical approaches, and innovative findings. The sample size in NEAR will be large enough to incentivize and facilitate the development of new methods for data collection using modern IT applications.

Societal relevance. WHO and the G8 industrialized nations have identified dementia and disability as a global public health priority. In line with their recommendations, NEAR seeks to identify intervention strategies to delay onset and progression of these disorders to help reduce their societal burden. In addition, NEAR will enable us to quantify the future economic and societal burden of age-related disorders and provide evidence for policymakers to better allocate resources and optimize care.

Relevance for national and international innovation. NEAR has great potential to contribute to innovation by enhancing our knowledge and its implementation in the public health, clinical, and private sectors. It can contribute to social innovation by providing scientific evidence regarding the integrated delivery of care services. NEAR will give us the opportunity to develop new biomarkers and treatments for specific diseases that can lead to clinically relevant innovations. Additionally, NEAR can be used to develop and validate specific applications to predict and monitor not only disorders such as dementia and multimorbidity but also drug treatments. These web-based tools can be used by patients, thus enhancing people's participation in health care, from prevention to long-term care and rehabilitation.

Contribution to competence development. The NEAR co-founders are all well-known researchers in the field of aging who come from different backgrounds and are active at six major universities in Sweden. This diversity provides the inspiring and interactive environment necessary to generate novel contributions and stimulate future research. NEAR will provide a platform for scientific exchange and communication among PhD students, postdocs, and junior researchers, and thus help educate and train younger generations of aging researchers in Sweden. Via their collaboration with the National Graduate School for Aging Research (SWEAH) at Lund University (already supported by VR), the NEAR co-founders will develop a plan for using the infrastructure in education.