UK Dementia Research Institute

Diversity and dementia

How is research reducing health disparities?

Report (published September 2022)

900k

people are living with dementia in the UK and this is expected to grow to 1.6m by 2040. Worldwide this figure is close to 50m and set to triple by 2050[1]

1 in 3

people born today will develop dementia in their lifetime[2]

£34.7bn

is spent each year on dementia - equivalent to nearly a quarter of the NHS budget [3,4]

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disease-modifying treatments available to stop or slow the progression of dementia

The statistics are clear: dementia is one of our greatest health challenges, and it's growing at an alarming rate. But these numbers alone do not reveal the true impact of dementia on society.

To understand this, we need to consider the role of health inequalities. There is evidence that certain subgroups of the population have a higher risk of developing dementia than others.[5–7] Age is of course the most important risk factor, with the chance of developing dementia increasing to one in six over the age of 85 (although dementia affects younger people too: in the UK there are over 42,000 people with early-onset dementia (EOD), which is highly heritable).[7–9] Innate characteristics like sex and ethnicity also play an important role in determining dementia risk: more women die of dementia than men (for reasons more complex than women simply living longer)[10] and dementia is more prevalent in Black and South Asian ethnic groups than white populations.[6,7] Prevalence also increases among people with intellectual disabilities such as Down syndrome and symptoms appear earlier[11,12]. Finally, dementia risk is increased by a number of environmental and lifestyle factors, such as air pollution or lack of physical activity, which are strongly linked to socio-economic status.[13,14]

The reasons for these disparities are complex. Our health is determined by a number of interacting factors and influences, ranging from innate characteristics to the socioeconomic, cultural and environmental conditions in which we live.[15] These factors do not only influence our risk of developing a certain disease, but may also affect our chance of getting a diagnosis, the efficacy of a treatment, or the likelihood of side effects from a drug.[16–18] And they affect our brains just as they do the rest of our bodies.

In the UK, health inequity has been thrown into sharp relief by the Covid-19 pandemic, which has claimed a disproportionately high number of Black and minority ethnic lives.[19,20] In his position as Secretary of State for Health and Social Care, Sajid Javid MP responded to this by ordering an independent review into racial bias in medical equipment, vowing to *"close the chasms that the pandemic has exposed"*.[21] The government has also committed to reducing health inequalities as part of its levelling up agenda, through a health disparities white paper.[22]

Much of the conversation about how to tackle the UK's health inequity rightly focuses on public services and clinical practice, especially our NHS. However, what we really need in dementia is new treatments, and we need to be sure that those treatments will help those who need them most. We also need to understand what puts certain groups at higher risk, and how best to prevent disease. To achieve that, we need to go right back to the science itself. We need to understand how and why different groups are affected differently by the same diseases, so that we can target interventions where they are most needed and maximise their benefit. We must reject longstanding biases in scientific research, and instead innovate in the name of inclusivity.

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Gillian Keegan MP meets participants in the Minder trial developed by the UK DRI Care Research & Technology Centre.

1. Ensuring biological diversity in our science

Neuroscientists have long been aware of structural and functional differences between male and female brains, and there is growing evidence that the biological pathways underlying neurodegenerative disease vary by ethnicity.[23–25] Despite these differences, it has historically been considered too challenging to incorporate diversity into scientific study designs. Mouse models in neuroscience, for example, have traditionally used only male mice, due to an assumption – now debunked – that female rodents increase variability due to their hormonal cycle.[25–27] Meanwhile, large-scale genomic studies of Alzheimer's disease have been primarily conducted in white populations.[24]

This lack of diversity has been acknowledged to lead to translational failure when it comes to drug development.[16,28] Just as biological disease pathways differ between populations, we cannot assume that all groups will respond similarly to a particular drug. In fact, there is strong evidence women metabolise drugs differently.[18,29] In the US, 8 out of 10 drugs withdrawn from the market in a 3-year period were due to significant health risks for women.[16]

To ensure this does not happen in dementia, we need to understand the nuances of the biological pathways of disease in different groups, and build diversity into our science from the beginning.

At the UK Dementia Research Institute (UK DRI), it is our policy that both sexes should be used in all pre-clinical work – including mouse models and cell lines – and that the sexes should be balanced. This must always be the case unless there is a compelling reason to include only one sex (e.g. studying a genetic form of disease that is linked to the X or Y chromosome). Our researchers are supported to meet this stipulation with expert advice, tailored support on experimental design, access to resources via a dedicated portal, and an informal internal review process.

"The problem with using only one sex in mouse models has been clearly documented. There's a failure of translation because of that flaw in the pre-clinical work.

At the UK DRI we've made it the default to study both sexes. And we help our researchers every step of the way to meet that."

Dr Frances Wiseman
UK DRI Programme Leader for Animal Models

Professor Tara Spires-Jones at the UK DRI's internal conference in 2019.

Professor Tara Spires-Jones (UK DRI Group Leader at Edinburgh) advocates for good practice in this area beyond the UK DRI through her editing, teaching, and work with the British Neuroscience Association (BNA). As Founding Editor in Chief at Brain Communications, Spires-Jones works to promote credibility through her editorials,[27] and by requiring that both sexes should be used in pre-clinical work for a paper to be accepted (unless there is strong scientific rationale for inclusion of only one sex). In her role teaching neuroscience students at Edinburgh University, Spires-Jones instils an ethos of inclusion from the start. And as President-Elect of the BNA, she campaigns for diversity to be considered a marker of credibility in research.

"I feel strongly that we need to instil an ethos in young researchers that reproducibility, diversity and inclusion are paramount. We need to make sure everything neuroscience discovers is relevant for everyone. That's the kind of thing I'm trying to get the next generation of researchers to think about from the start."

2x

According to research, Black people are approximately twice as likely than white people in the same community to develop Alzheimer's disease, and there is evidence that the biological pathways of disease differ by ethnicity.[24] Despite this, large-scale genomic studies of Alzheimer's risk have mainly been conducted in white populations, with the consequence that these differences are not well understood.[24]

Professor John Hardy (UK DRI Group Leader at UCL) is a world-leading neuro-geneticist, specialising in the genetic analysis of Alzheimer's disease and Parkinson's disease. Working with Dr Mie Rizig (UCL) and Prof Njideka Okubadejo (University of Lagos), he is conducting genetic association studies in Nigeria and across Africa, to better understand how genetic risk varies by ethnicity.

Understanding the genetic basis of disease in different ethnicities will help us predict within ethnic groups who is at greater risk of developing disease, facilitating earlier diagnosis and, eventually, early access to therapies. This research also deepens our understanding of the disease for everybody.

"At the moment, we can predict amongst white Europeans who will get Alzheimer's disease with accuracy of about 80%. But with regard to people with Black African heritage it's only about 60%, and in Chinese populations we're only able to predict it to about 70%. So we need to get better.

"Not only is this important for decreasing health disparities but studying the disease in different populations will help us all. We might find different genes that influence the disease risk or different mutations, which help fill in the holes in our knowledge about the development of these diseases in general."

Lagos state, Nigeria, where genetic studies for Alzheimer's and Parkinson's are being conducted.

2. Innovating to diversify clinical trials

Clinical trials provide critical evidence for the safety and efficacy of new drugs in humans, and are essential for the development of future therapies. To produce generalisable results – and avoid approving drugs that are less effective or less safe in certain populations – trial participants must be representative. However, historically this has not been the case, with, for example, ethnic minorities underrepresented.[30] In the UK, this remained true during the pandemic, despite the disproportionate impact of Covid-19 on ethnic minority groups.[31] In dementia, women are underrepresented in trials, despite the increased prevalence of disease.[32,33]

People may be prevented from participating in clinical trials for a number of reasons, including lack of information, lack of trust, limitations on resources, pragmatic barriers such as the requirement to travel or give up time, or because they do not meet strict inclusion criteria built into the study design.[30] This creates a gap in knowledge about the groups who are excluded, which in turn perpetuates health inequity.

Researchers in the UK DRI are working to address challenges of trial design, resources, trust, information and geographical distance in order to widen the accessibility of our clinical trials to a wider section of our society.

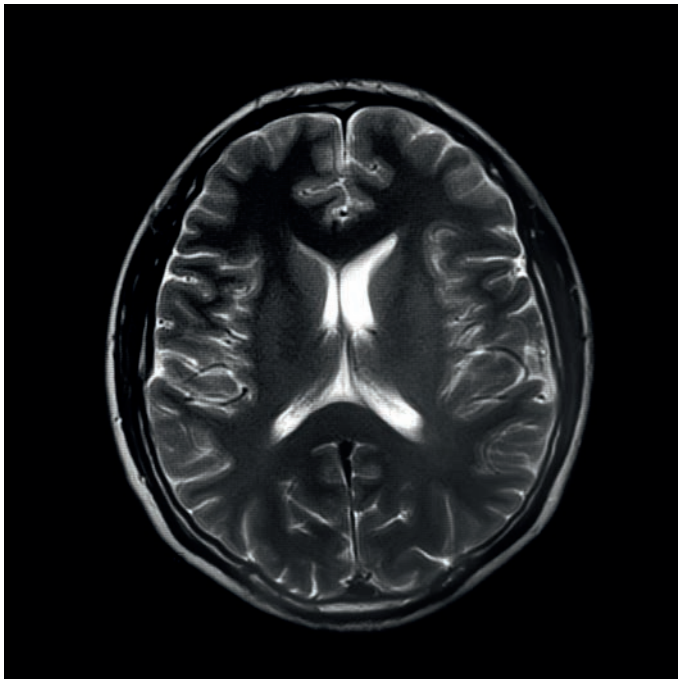
Launch of the UK DRI Care Research & Technology Centre (May 2022): Designer Sophie Horrocks disusses the patient-centred development of innovative new technology.

Sophie Horrocks from the Helix centre is working to build partnerships with local community groups to disseminate information, build trust in research, and offer opportunities to get involved in research. As well as supporting a patient-centred design process at the UK DRI Care Research & Technology Centre, Horrocks is also producing guidelines for UK DRI researchers to help ensure their trials are accessible.

"Working in dementia presents unique challenges. It's a progressive condition, people's circumstances change. We have to be conscious of that. We think working with community organisers can help to overcome this. It's about building a community. We are stepping into a trusted space, a place where they feel comfortable."

The B-RAPIDD study, co-led by **Professor Nick Fox** (UK DRI Group Leader at UCL), is seeking to "democratise dementia diagnosis" by transforming how a diagnosis is made to make it more accessible and cost effective. Currently, a secure diagnosis of Alzheimer's disease typically requires a brain scan and a measure of amyloid protein pathology (usually from cerebrospinal fluid (CSF) or PET scans, both of which are invasive and expensive to provide) – and these are a prerequisite for most trials.

Working with **Professor Henrik Zetterberg** (UK DRI Group Leader at UCL), Fox is testing whether blood biomarkers, which are much cheaper and less invasive, could replace CSF, removing the need for a lumbar puncture or a PET scan. Fox and Zetterberg are also harnessing advances in MRI technology to reduce typical scanning time from 30 minutes to 5-7 minutes, dramatically increasing the potential throughput of the UK's scanning capacity. These two innovations, taken together, will make diagnosis accessible to a much larger group of people with dementia, facilitating timely and accurate enrolment into clinical trials. Professor Fox says:



UK DRI researchers aim to reduce MRI scanning duration which will help enrolment into clinical trials for dementia.

"There are lots of underrepresented groups in studies – racial and cultural groups, as well as those who experience poverty. Why is it important? It's important for social justice. People who are part of clinical trials have better outcomes than people who are not, even if they are given the placebo. In terms of applied research, deeply thinking about what's acceptable to people in terms of a diagnostic process, in terms of disease-modifying trials… we clearly are missing huge number of people who would potentially benefit from a licensed therapy. So representation is really, really important, both for finding treatments and then ultimately delivering them in a clinical service."

The opening of the first MND-SMART trial at the Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, in March 2020. First trial participant Alan Gray with his wife Beverley alongside, Director of the MND-SMART Clinical Trial, Professor Siddharthan Chandran and MND Nurse Consultant, Judy Newton.

Professor Siddharthan Chandran (UK DRI Group Leader at Edinburgh) is working to diversify and expand access to clinical trials for motor neurone disease (MND). Chandran and a team of internationally leading scientists, clinician-triallists and statisticians (MRC CTU at UCL) have developed MND-SMART (Motor Neuron Disease – Systematic Multi-arm Adaptive Randomised Trial), the first UK-wide, multi-arm, multi-stage (MAMS) adaptive platform trial for MND, and one of only two MAMS studies for MND globally. Chandran says innovation in MND trials is the key to finding new drugs:

"Our job is to try to change outcomes for people. If there's a gain to be made, I think it's in clinical trials. We need to have the same level of imagination and investment in trial designs as we do in discovery science, and run the two in parallel and indeed feed each other."

"I don't want any patient driving past three hospitals to access a trial at the fourth."

The team is establishing centres of trial expertise across the UK, to improve access regardless of postcode. To include communities that have not historically participated, Chandran and the team are investing in bespoke, local resources, working closely with local researchers and clinicians. A particular effort is being made to build teams in areas that are ethnically diverse or have low socio-economic status.

The trials themselves are designed with broad inclusion in mind. Treatment protocols are appropriate to the patients' needs, such as liquid medication instead of tablets for those with difficulty swallowing. Inclusion criteria have been expanded to enable more patients to participate without losing study power. Chandran and the team can thus extract a signal even with a clinically diverse group of participants.

3. Pioneering accessible new therapies

Any new therapy developed by our scientists needs to be practical and affordable to implement. To confront health inequalities in dementia, it is essential that we consider the accessibility, scalability and affordability of our innovations while they are in development. The UK DRI's mission is to make a difference to as many people as possible, even if that presents additional challenges in our science.

Dr Nir Grossman (UK DRI Group Leader at Imperial) is pioneering a non-invasive deep brain stimulation therapy, with the potential to be a new and innovative treatment for Alzheimer's disease. Temporal interference (TI) is a technique that manipulates deep brain activity via electrodes attached to the scalp. Unlike other brain stimulation treatments, TI is non-invasive and does not require surgery, meaning it will be more affordable to provide, scalable, and acceptable to people with dementia.

Having proven the concept in the lab, Grossman and his team are consulting with people living with dementia and re-engineering the technology to make it suitable for treatment at home. They are running a series of participant workshops to explore usability and acceptability of the device. Grossman believes this is the only way to make the treatment truly accessible.

Engineer Dr Nir Grossman showcases temporal interference technology for non-invasive treatment of Alzheimer's disease.

"Talking to participants, it was clear from the start that the treatment needs to happen at home. Otherwise it will only be available to those who are more well-off – people who can afford transportation and have care support to bring them to hospital every day. We want to reach the whole population, including those with minimal support. To achieve that, we're re-engineering the whole thing."

UK DRI researchers Ketevan Alania and Julia Borella working on non-invasive technology for dementia. The team run workshops to gain insight from people with lived experience of dementia.

Speaking about her involvement in the latest workshop, **Carroll Siu**, who has Parkinson's disease, said:

"I was part of a group of people living with neurodegenerative conditions who were invited to join a workshop to consider ways to ensure that new technology is accessible and suitable for a wide range of people to use. There was a true sense of patient engagement as people with Parkinson's, multiple sclerosis and carers of people with Alzheimer's were there with researchers, clinicians and representatives from charitable organisations in round table discussions as part of the collaborative process of co-creation in research."

4. Addressing rare and under-researched forms of dementia

Rarer forms of dementia, or those that only affect certain groups of the population, are typically under-recognised and under-researched compared to more common forms such as Alzheimer's disease or vascular dementia. At the UK DRI, we are working to support people living with these rare forms of dementia right now, and to fill the knowledge gap of these diseases so that we can find new therapies in the future.

By analysing our genetics, we can learn more about the fundamental causes of conditions like early-onset Alzheimer's disease that lead to dementia.

Early-onset Alzheimer's disease (EOAD) causes dementia symptoms to emerge in people's 40s, 50s or 60s – and it can be inherited. It disrupts their ability to earn a living and can drive families into poverty. Due to its relative rarity, it is under-researched and families struggle to get appropriate support.

Professor Julie Williams (UK DRI Centre Director at Cardiff) is currently co-leading a major worldwide genome-wide association study on EOAD, with over 12,000 cases. The purpose of the study is to identify genes that may specifically affect early-onset cases, which will pave the way for new therapies. This may also give us clues about the mechanisms of late-onset Alzheimer's disease, deepening our understanding of the more common form of the condition.

Dr Frances Wiseman (UK DRI Group Leader at UCL) investigates Alzheimer's disease in individuals with Down syndrome (DS). An estimated 42,000 people have DS in England and Wales, and their lifetime risk of developing dementia is 90-100%.[11,12] Alzheimer's disease in Down syndrome (AD-DS) is the most commonly occurring genetic cause of early-onset dementia. But despite the high prevalence of dementia in this population there has been very little research into AD-DS, and people with DS are typically excluded from Alzheimer's disease trials.[35]

It is well documented that people with intellectual disabilities, including DS, often receive a poorer standard of healthcare compared to those without, and may experience worse health outcomes as a result.[36] During the Covid-19 pandemic, the mortality rate among adults with DS in the UK was estimated to be around ten times higher than among those with no intellectual disability, and despite being more severely ill at admission, people with intellectual disability with Covid-19 experienced significant disparities in access to life-saving treatment such as intubation.[37–39]

50% of individuals with Down syndrome will have a dementia diagnosis by the age of 50.

Wiseman is addressing the knowledge gap in AD-DS by uncovering DS-related causes of dementia. She and her team recently demonstrated the role of a gene on chromosome 21 in driving disease progression, and hope to identify more key components causing neurodegeneration in DS.

"Historically, the area of medical research for people with intellectual disability has been underfunded globally. So, for example, people with Down syndrome are excluded from clinical trials for Alzheimer's disease, even though around 50% of those individuals will have a dementia diagnosis by the age of 50. So I saw an opportunity to make a significant contribution to improve health outcomes of this important group of individuals."

Professor Nick Fox running a cognitive clinic for people living with early-onset dementia at the Dementia Research Centre in UCL, London.

UK DRI researchers are also working to support people living with early-onset dementia today. **Professor Nick Fox** (UK DRI Group Leader at UCL) co-founded Rare Dementia Support – www.raredementiasupport.org – which has grown from a small service providing advice and peer support by volunteer researchers and clinicians to a thriving service with 10 staff, 4,000 members and 20 regional groups. Rare Dementia Support provides social, emotional and practical support with research and training about rare, genetic and young-onset dementias. It facilitates peer-to-peer support networks so that people feel supported in their communities, and works to raise awareness about rare forms of dementia – and how to get involved in research and trials.

5. Exposing the impact of social inequality on brain health

Dementia is a condition for which no disease-modifying therapies are available. However, we can take action to reduce and slow these diseases by tackling the factors that increase our risk. A recent report in The Lancet found that modifiable risk factors account for about 40% of worldwide dementias.[40] By addressing environmental and lifestyle factors that contribute to dementia, we can in some cases prevent or slow cognitive decline before symptoms develop.

Prevention is crucial to reducing health inequalities in dementia, since many of the known risk factors are socially patterned, meaning that individuals who are disadvantaged in society may also have a higher risk of becoming ill.[13] At the UK DRI, our researchers are studying the environmental and lifestyle factors that increase our risk of disease, so that we can target preventative interventions where they will be most effective.

Professor Paul Elliott (UK DRI Group Leader at Imperial), a world expert in public health and epidemiology, is researching how environmental, lifestyle, genetic and metabolic risk factors interact to determine our likelihood of developing dementia. The relationship between these factors is highly complex, but by using powerful technologies and sophisticated data analyses, Elliott hopes to uncover subtle shifts, which will reveal new insights about these diseases, how best to prevent them, and how we can reduce health disparities.

Elliott leads the Airwave study, which examines the health of the UK police force and collects data on a wide range of biological, lifestyle and environmental factors, ranging from genetic information to whether a person uses alcohol or does shift work. Just as in the well-known "Whitehall study", the police force has a strong hierarchy, which means that the role of socio-economic status can be better understood.[43]

Alcohol consumption is one of 12 modifiable risk factors which evidence suggests contributes to 40% of worldwide dementia cases.[40]

Poor cardiovascular health is linked to lower socioeconomic status in high-income countries,[13] and all major vascular risk factors are increased in people at socioeconomic disadvantage in adulthood. Heart disease is also a known risk factor for dementia. The UK DRI brings together multidisciplinary researchers to examine the link between heart and brain health. A deeper understanding of this connection will enable effective targeting of measures to reduce dementia risk, such as lifestyle changes and prescription medications already available for cardiovascular disease.

Clinical scientist Professor Joanna Wardlaw investigates vascular contributions to neurodegeneration in the search for new treatments.

Professor Joanna Wardlaw (UK DRI Group Leader at Edinburgh) leads the Vascular research theme at the UK DRI, bringing together clinical and preclinical expertise to explore opportunities for intervention. The interdisciplinary group investigates the heart-brain connection from multiple angles, including vascular contributions to neurodegeneration in patient cohorts, and the mechanisms behind vascular and blood-brain barrier dysfunction during ageing and disease.

Wardlaw and her team are conducting multiple studies in this area. In a clinical study of 230 patients at high risk for vascular dementia, they are determining factors, including adult and early life socioeconomic status, that influence cognitive decline.[41] The team has even been able to assess the influence of early life factors, including socioeconomics, on the risk of small vessel disease which is the main vascular cause of dementia.[42]

In addition to this work to understand causes, Wardlaw and her team are studying interventions to prevent vascular dementia. Based on their work to understand vascular brain injury, they are running one of the few randomised clinical trials anywhere in the world that uses drugs to prevent vascular causes of dementia, known as the LACI trials. Primary results will be reported later in 2022.

A recent review of scientific literature has concluded that there is sufficient evidence to suggest pollution contributes to dementia risk. [14]

Professor Nick Fox (UK DRI Group Leader at UCL) was part of a small working group commissioned by the Committee on the Medical Effects of Air Pollutants (COMEAP), to consider and advise the government on the effects of air pollutants on dementia risk. The group conducted a comprehensive review of the available research and concluded there is sufficient evidence to say that pollutants increase dementia risk.[14] This is important because air pollution is not evenly distributed: high pollution levels are more likely to be experienced by communities with more ethnic diversity or a lower socio-economic status.[44,45] Exposure to air pollution is difficult for individuals to avoid. Rather, structural, societal and policy changes are necessary to reduce this risk factor, which disproportionately impacts certain populations.

Conclusion

Dementia does not impact everyone equally. In the UK, certain subgroups of the population are at higher risk of developing the condition, and this risk is impacted by factors including sex, ethnicity and socio-economic status. With no disease-modifying therapies available, there is limited scope to address health inequity in dementia through healthcare alone. To do this, we need to go back to the science and find new ways to prevent, diagnose and treat dementia that help those who need it most.

The UK DRI is making strides in this area, but there is more to do. Rarer forms of dementia remain under-researched, as is the genetic role of ethnicity in determining dementia risk. These are crucial avenues for reducing health disparities and must be better understood. New innovations in data science and informatics create further opportunities to understand diversity in dementia and connect patient populations with epidemiological studies on lifestyle and environmental risks.

Lastly, we need to ensure we have diversity in the scientific workforce itself, to ensure a breadth of thought and approach in our research. The workforce is beyond the scope of this report, but there is much to be done to ensure that the diversity of our research teams represents the diversity of communities affected by dementia, a challenge we are taking on with a taskforce and new strategy for Equity, Diversity and Inclusion (EDI). Only then will we be in a position to overcome disparities in dementia for good.

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