DOMINO-HD: A 12-month observational cohort study of lifestyle factors in people with Huntington's disease

Philippa Morgan-Jones[1,2], Cheney J.G Drew[1], Laura Mills[1], Nigel Kirby[1], Philip Pallmann[1], Astri Arnesen[3], Esther Cubo[4], Beth Ann Griffin[5], Hans H. Jung[6], Bernhard Landwehrmeyer[7], Madeleine Lowery[8], Grzegorz Witkowski[9] and Monica Busse[1]

[1]Centre for Trials Research, Cardiff University, UK; [2]Cardiff School of Engineering, Cardiff University, UK; [3]European Huntington Association; [4]Hospital Universitario of Burgos, Spain; [5]RAND Corporation, Arlington, VA, USA; [6]University Hospital and University of Zurich, Switzerland; [7]University of Ulm, Germany; [8]University College Dublin and Insight Centre for Data Analytics, University College Dublin, Ireland; [9]Institute of Psychiatry and Neurology, Warsaw, Poland.

(correspondence email: dominohd@cardiff.ac.uk)

European Huntington's Disease Network (EHDN) 2021 Remote Meeting

Background

- Environmental factors such as lifestyle behaviours have emerged as potential moderators of Huntington's disease (HD) onset and progression[1, 2].

- Digital monitoring devices offer an exciting opportunity to further investigate the role of lifestyle in disease modification but their long-term use in clinical HD populations has not yet been sufficiently explored.

- The hypothesis underpinning this study is that we can influence prognosis in HD through the use of digital technology[3] as a naturalistic, 'real world' approach to symptom detection and environmental modification.

[1] Mo et al. (2015). *Neurosci Biobehav Rev*. 52: 178-92.

[2] Fritz et al. (2017*). J Huntingtons Dis*. 6 (3): 217-235.

[3] Herrington et al. (2018). *Clinical Trials*, 15 (3): 313-315

IDOMINOHD

Aims/Goals

Aim:

Investigate the use of digital technologies in a longitudinal observational study to inform our understanding of the contribution of multi-domain lifestyle and genetic factors in the progression of HD.

IDOMINOHD

Aims/Goals

Our specific research questions are:

1. How do physical activity, sleep, dietary intake and identified genetic modifiers inform disease outcomes over 12-months?
2. How can digital sensing devices provide objective assessments of physical activity and function that are both clinically meaningful and acceptable to HD participants?
3. Can novel quantitative clinical assessments provide sensitive, objective markers of disease progression?
4. What are the essential requirements for a multi-modal life-style intervention where visualisation of naturalistic patient generated data derived through digital, sensor-based assessment is likely to be a key feature?
5. How can we support intervention implementation at the individual and care provider level and across a variety of social and cultural settings?

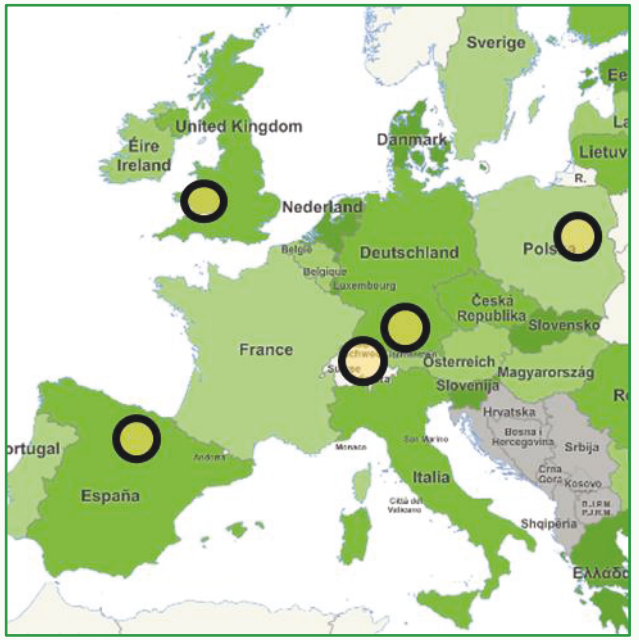
IDOMINOHD

Methods

Recruitment strategy

- Target of 300-450 participants with early to mid-stage HD across 5 clinical sites:

  - Cardiff, UK
  - Burgos, Spain
  - Warsaw, Poland
  - Zurich, Switzerland
  - Ulm, Germany



IDOMINOHD

Methods

Participant inclusion criteria:

- ✓ Diagnosis of HD confirmed by genetic testing.
- ✓ Above the age of 18.
- ✓ Diagnostic confidence level (DCL) ≥2 which can include both pre-motor [late prodromal] or motor manifest HD.
- ✓ Self-ambulatory.
- ✓ A participant (current or newly enrolled) in the Enroll-HD study (with a preference for those who have been genotyped in GWAS3-5 or are to be genotyped in GWAS6).

IDOMINOHD

Methods

Participant exclusion criteria:

- ✓ Diagnosis of juvenile onset HD.
- ✓ History of co-morbid neurological conditions such as multiple sclerosis or stroke.
- ✓ Acute (within 1 month) orthopaedic conditions e.g. ankle sprain or fracture.
- ✓ Severe medical conditions such as unstable or progressive heart disease, uncontrolled diabetes, severe liver, kidney or thyroid dysfunction or similar medical conditions.
- ✓ Any acute or unstable psychiatric conditions.
- ✓ Unable to tolerate long-term wear of an activity monitor.
- ✓ Inability or unwillingness of participant to give written informed consent.
- ✓ No access to a smartphone.
- ✓ Not willing to install, or allow the research team to install Apps on their smartphone related to the study.

Methods

Data collection protocol across all clinical sites:

Baseline DOMINO-HD clinical visit

Coinciding with Annual Enroll-HD Visit (maximum of 8 weeks between visits)

12-month in-home monitoring period

12-month follow up DOMINO-HD clinical visit

Coinciding with Annual Enroll-HD Visit (maximum of 8 weeks between visits)

DOMINOHD

Methods

Data collection protocol across all clinical sites:

Baseline and 12-month follow up DOMINO-HD clinical visits

The following constructs are measured/assessed:

- Patient-reported clinical symptoms
- Nutrition
- Motor and dual task function
- Speech
- Apathy
- Physical activity, mental activity and sleep
- Anthropometrics

The following optional constructs may also be measured/assessed:

- Eye movements, relationships and assessment acceptability

Assessments from the DOMINO-HD baseline and 12-month follow up visits will be linked to the relevant visit based Enroll-HD data to obtain measures of clinical symptoms and progression.

The full Enroll-HD protocol can be found at: https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf

A subset of relevant Enroll-HD measures will be requested.

Enroll-HD

DOMINOHD

Methods

Data collection protocol across all clinical sites:

12-month in-home monitoring period
• Wear a Fitbit Charge 4 on the wrist as regularly as possible throughout the monitoring period to longitudinally measure physical activity and sleep patterns. • Receive weekly SMS text messages reminding participants to wear their device and a phone call follow up if >50% of Fitbit data is missing over a month period.

IDOMINOHD

Methods

Statistical Analysis Plan:

Our approach will include predictive outcomes modelling to identify modifiable environmental factors that influence HD outcomes.

Derivation of genetic liability measures:

- GWAS data will be used to derive polygenic measures of genetic risk for relevant traits, including age at motor onset and progression in HD along with psychiatric disorders.
- These will be tested for association with the progression measures, both directly and as interactions with the measures of physical activity, sleep and diet. They will also be used in analyses of causality.

Analyses of causality:

- Propensity score weighting methodology will be applied to robustly examine the causal effect relationship between multi-domain (sleep, physical activity and nutrition) environment measures and composite measures of HD severity and progression.

Analyses of 12-month DOMINO-HD longitudinal data:

- A summary overview of physical activity, diet and sleep data will be determined across the cohort.
- A summary of user acceptability will be generated based on user evaluations.
- Summary statistics for the Fitbit physical activity and sleep metrics will be reported and machine learning algorithms applied to identify any metrics that may be useful to predict disease progression.

DOMINOHD

Results

- Recruitment as been significantly impacted by Covid-19, resulting in recruitment delays of 10 months.

- As of 18th August 2021, a total of 45 participants have been recruited across all clinical sites:
  - Burgos: 22
  - Warsaw: 12
  - Cardiff: 10
  - Zurich: 1
  - Ulm: 0

- The recruitment period is planned to continue until March 2022.

Conclusion

- Successful collection of longitudinal lifestyle data, combined with functional clinical measures and genetic factors will allow, for the first time, the investigation of causal relationships between environmental and genetic modifiers with HD progression.

- We can then use the information generated to design lifestyle interventions aimed at improving quality of life and prognosis in HD.

IDOMINOHD

Acknowledgements

This research is part of the Multi-Domain lifestyles Targets for Improving Prognosis in Huntington's Disease (DOMINO-HD) Consortium with partners in Cardiff University, University College Dublin, Ulm University, University Hospital Zurich, Hospital Universitario Burgos, the Institute of Psychiatry and Neurology, Warsaw and RAND Corporation.

DOMINO-HD is funded though the EU joint program for Neurodegenerative Disease Research as part of the JPND funding call in to Health and Social Care (2019) with funding from Alzheimer's Society, Secretary of State for Health and Social Care, Health and Care Research Wales, Public Health Agency Northern Ireland, Jacques and Gloria Gossweiler Foundation, Bundesministerium für Bildung und Forschung, Narodowe Centrum Badań i Rozwoju, Swiss National Science Foundation (SNF), 32ND30_185548 and Health Research Board (JPND-HSC-2018-003).