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Identifying pathways to the prevention of dementia: the Netherlands consortium of dementia cohorts

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Abstract

Background Aggregation of cohort data increases precision for studying neurodegenerative disease pathways, but efforts to combine data and expertise are often hampered by infrastructural, ethical and legal considerations. We aimed to unite various cohort studies in the Netherlands to enhance research infrastructure and facilitate research on dementia etiology and its public health implications.

Methods The Netherlands Consortium of Dementia Cohorts (NCDC) includes participants with initially no established cognitive impairment from 9 Dutch cohorts: the Amsterdam Dementia Cohort (ADC), Doetinchem Cohort Study (DCS), European Medical Information Framework for Alzheimer's Disease (EMIF-AD), Longitudinal Aging Study Amsterdam (LASA), the Leiden Longevity Study (LLS), The Maastricht Study, the Memolife substudy of the Lifelines cohort, Rotterdam Study and Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study. The objectives of NCDC are to improve data infrastructure and access to cohorts related to aging and dementia, investigate the role of Alzheimer's disease and vascular pathology in the development of dementia and estimate the public health impact of established dementia risk factors by assessing their relative contribution to the population burden of dementia.

Results We increased the findability, accessibility, interoperability and reusability (FAIR) status of the cohorts through harmonization of data across cohorts, implementation of medical imaging repositories for scan management, implementation of the Personal Health Train infrastructure and provision of meta-data in existing cohort catalogues. We established the ethical and legal frameworks required for federated and pooled analyses and performed the first remote federated data analyses using the Personal Health Train infrastructure. To determine biomarkers of Alzheimer's

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disease, endothelial dysfunction and inflammation, 2554 plasma samples were analyzed centrally. Federated, pooled, and coordinated meta-analyses have led to multiple publications in the context of NCDC.

Conclusion The combination of population-based and clinical cohorts, the coordinated assessment of plasma markers in previously collected samples and implementation and use of the Personal Health Train infrastructure for federated analysis are both feasible and promising for future collaborative efforts.

Keywords Netherlands Consortium of Dementia Cohorts, Personal Health Train, FAIR, Data infrastructure, Data access, Harmonization, Alzheimer's disease, Vascular pathology, Dementia prevention, Cohort studies

Introduction

The most common types of dementia are Alzheimer's disease dementia, characterized by accumulation of the amyloid and tau protein, and vascular dementia, characterized by hemorrhagic and ischemic brain lesions [1]. Often, dementia has multiple underlying pathologies [2]. To provide enough power to study disease pathways in an integrative manner, considering multiple pathological mechanisms as well as genetic and environmental factors, large-scale data analyses are needed. This objective can be achieved by combining data from multiple cohorts. However, infrastructural, ethical and legal considerations often complicate this process and preclude the joining of expertise and strengths of individual studies.

The overall aim of the Netherlands Consortium for Dementia Cohorts (NCDC) project is to unravel the pathophysiology of dementia and find clues for primary prevention through joint analysis of data from Dutch cohorts in the field of aging and dementia. By joining expertise, we moreover seek to translate this knowledge towards development of improved preventive strategies and meaningful public health policy. Specifically, the objectives of NCDC are infrastructural, scientific, and public-health oriented: (1) to improve data infrastructure and data access (infrastructural), (2) to investigate the role of Alzheimer's disease and vascular pathology in the development of cognitive decline and dementia amongst others by using plasma markers of vascular and Alzheimer's disease pathology (scientific) and (3) to estimate the public health impact of established dementia risk factors by assessing their relative contribution to the population burden of dementia (public health).

In this paper, we describe the methodology used in setting up the NCDC consortium and provide an overview of the results and output to date.

Methods

Governance structure

NCDC received funding in the context of Deltaplan Dementie from the Netherlands Organisation for Health Research and Development (ZonMw) Memorabel and Alzheimer Nederland. The project started in September 2018 and will run until July 2025. Objectives were operationalized through the formation of work packages (WP; summarized in Supplemental Fig. 1). Governance of data management and scientific content lies with an executive board that includes representatives of all participating cohorts. A user committee was formed to help monitor progress and provide guidance on the design, results and implementation of the work conducted within NCDC. The committee is comprised of general practitioners, memory clinic professionals, study participants and representatives from industry, pharma, health insurance providers, Dutch Health Research Infrastructure (Health-RI), a Dutch dementia prevention trial (The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability – the Netherlands or FINGER-NL), Alzheimer Nederland and the Ministry of Health, Welfare and Sport.

Data collection and availability

Ongoing Dutch population-based and clinical cohort studies focused on aging and dementia were selected and invited to participate based on the criteria detailed in Table 1. Nine cohorts were included: the Amsterdam Dementia Cohort (ADC), Doetinchem Cohort Study (DCS), European Medical Information Framework for Alzheimer's Disease (EMIF-AD), Longitudinal Aging Study Amsterdam (LASA), the Leiden Longevity Study (LLS), The Maastricht Study, the Memolife substudy of the Lifelines cohort, Rotterdam Study and Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study. These cohorts were initiated between 1987 and 2021 and have available follow-up data for up to 17 visits and 23 years. Cohort descriptions are provided in Table 2.

After selection of cohorts, we initiated the establishment of the ethical and legal frameworks and infrastructure needed to allow for individual participant data meta-analysis within the consortium. We took both a two-step (analyses are performed separately per cohort and results are pooled; federated analysis) and one-step meta-analysis approach (analyses are performed using one statistical model that accounts for clustering; pooled analysis). Both the two-step and one-step approach require harmonization of the data used in the analyses. To inform these harmonization efforts, we created a minimal dataset, containing a list of variables relevant to

Table 1 Inclusion criteria for NCDC cohorts

1	Inclusion of individuals without dementia at baseline.
2	Studies should not have a single focus on rare genetic forms of dementia
3	Baseline or follow-up data available after age 60
4	Detailed and repeated assessments of cognitive function or specialist verified diagnosis of dementia and its subtypes
5	In addition, collection at baseline of at least 4 of the following modalities: (1) genetics, (2) vascular risk factors, (3) psychosocial risk factors, (4) metabolomics or inflammation markers, (5) amyloid pathology (plasma, CSF, PET), (6) vascular pathology (MRI), (7) brain atrophy and connectivity (MRI), (8) comorbidities (e.g. stroke, depression, coronary heart disease)
6	Ongoing data collection. Cohorts with a closed follow-up that meet all other criteria could participate as an affiliated cohort
7	Existing infrastructure for systematic follow-up of participants, i.e. on health status, including dementia and cognitive impairment
8	Investigators related to that cohort have a longstanding track-record in the field of dementia and Alzheimer's disease

the analyses that are planned within NCDC (Appendix I). This list was based on the objectives for the scientific work packages (visualized in Supplemental Fig. 1) and spans several domains including demographics, cognition, lifestyle, comorbidities, MRI data, cerebrospinal fluid (CSF) biomarkers of amyloid and tau, positron emission tomography (PET) and plasma biomarkers. We subsequently made an overview of the availability, name and coding of the minimal dataset variables in each NCDC cohort. This allowed us to map all cohort variables to a central name and coding. The central coding was based on the EMIF-AD ontology, which is a free, open-source, collaborative ontology available through the Bioportal website [11]. The EMIF-AD ontology is specifically targeted at data collected in studies of cognitive aging and dementia and was developed based on large-scale studies and expert input. An example of the mapping for the education variable is provided in Supplemental Table **1** for illustration purposes.

Legal and technical aspects of data sharing

To ensure that all legal and ethical considerations for both federated as well as pooled analysis of data were met, legal representatives from all cohorts met to discuss requirements and address any additional considerations. These included ensuring that there was informed consent for the use of data in other studies and that this informed consent was up to date. Ultimately, two Joint Controllership Agreement (JCA) were signed, one JCA for the federated and one JCA for the pooled analyses. The JCA's specify the responsibilities and roles of each party with regard to data security and privacy, include agreements on how data will be accessed and contain a brief but comprehensive summary of the analyses that will be performed within the NCDC consortium. It is important to note that these contracts allow for data exchange between NCDC consortium partners only. Proposals for research projects have to be approved by the executive board and principal investigators of the respective cohorts before they can be executed. Per the authorship agreements established within the consortium, cohort representatives will be acknowledged in any resulting publications.

Federated analyses

To allow for federated analyses, NCDC makes use of the privacy-by-design Personal Health Train (PHT) infrastructure [12]. The core strength of the PHT infrastructure is that data does not leave the host institution, thereby ensuring optimal data privacy and control of data. The PHT infrastructure consists of "stations" at each institute, where harmonized data is uploaded to a local server and "tracks" through which analytical algorithms and results of locally run analyses ("trains") can be exchanged. To establish the PHT infrastructure, the necessary software [13] was installed at each institute and the minimal dataset variables were harmonized to the Observational Medical Outcomes Partnership (OMOP) common data model (CDM) and uploaded to the PHT environment. OMOP is an open community standard for health data that was designed to help standardize the structure and content of observational data [14]. The PHT infrastructure will, in time, be made accessible to external researchers interested in working with NCDC data. To help facilitate analyses, medical imaging repositories for scan management will be implemented across cohorts.

Pooled analyses

For direct pooling of data, NCDC cohorts share subsets of data and variables relevant to the analyses planned within NCDC with Maastricht University, where it is stored centrally and securely in accordance with the regulations set out in the JCA. Contact persons are appointed at each site to facilitate this process and ensure that any required changes (e.g. due to withdrawal of informed consent) can be realized swiftly. Direct data sharing will be limited to data from the subset of participants for whom plasma biomarker data is available.

Table 2 Cohort Descriptions

Name	*Partner*	*Short Description*
Amsterdam Dementia Cohort (ADC)[3]	VUmc-AC	*Aim*: To study the causes and outcomes of neurodegenerative disorders *Setting*: Memory clinic *Start*: 2000 *Number of participants*:1041 *Data collection*: Clinical and cognitive data, MRI, EEG, blood, DNA, CSF AD biomarkers *Follow-up*: Annual follow-up (clinical)
Doetinchem Cohort Study (DCS)[4]	RIVM	*Aim*: To provide insight in changes over the life course in lifestyle, metabolic risk factors and health, and the relation between risk factors and disease *Setting*: Population-based *Start*: 1987 *Number of participants*: 6000 *Data collection*: Clinical and cognitive data, lifestyle data, cardiometabolomic data, metabolomic and genomic data *Follow-up*: Every 5 years
European Medical Information Framework for Alzheimer's Disease (EMIF-AD)[5]	VUmc-AC	*Aim*: To allow for large-scale research on biomarkers and risk factors for neurodegenerative disorders *Setting*: Population-based *Start*: 2018 *Number of participants*: 313 *Data collection*: Clinical and cognitive data, MRI, blood, DNA, PET *Follow-up*: Annual
Longitudinal Aging Study Amsterdam (LASA)[6, 7]	VUmc-APH	*Aim*: A longitudinal study on daily functioning and well-being of older persons, interdisciplinary *Setting*: Population-based *Start*: 1992 *Number of participants*: 5132 *Data collection*: Cognitive data, psychosocial data, blood, DNA *Follow-up*: Every 3–4 years
Leiden Longevity Study (LLS)[8]	LUMC	*Aim*: To study the determinants and biomarkers of healthy ageing and longevity *Setting*: Research cohort, a two-generational study *Start*:2003 *Number of participants*: 944 (90+), offspring (2415) *Data collection*: Clinical and cognitive data, MRI, data on environmental exposures, metabolomic and genomic data *Follow-up*:20 years
The Maastricht Study	MUMC-IG	*Aim*: To study the complications of type II diabetes *Setting*: Population-based *Start*: 2010 *Number of participants*: 9200 *Data collection*: Clinical and cognitive data, psychosocial data, plasma markers, MRI, DNA, lifestyle data *Follow-up*: Ongoing
Memolife substudy of Lifelines	UMCG	*Aim*: Investigating complex interactions between environmental, phenotypic and genomic factors in the development of chronic diseases and healthy aging. *Setting*: Population-based three-generation cohort *Start*:2006 *Number of participants*:281 *Data collection*: Clinical data, MRI, plasma, blood, urine, DNA *Follow-up*: Every 5 years

Table 2 (continued)

Name	*Partner*	*Short Description*
Rotterdam Study[9, 10]	EMC	*Aim*: To study the determinants, pre-clinical development and prognosis of chronic disease in the elderly *Setting*: Population-based *Start*:1990 *Number of participants*: 14.926 *Data collection*: Clinical and cognitive data, psychosocial data, functional outcome data, MRI, PET, data on environmental exposures, metabolomic and genomic data *Follow-up*: Every 3–4 years
Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study	UMCU	*Aim*: To investigate risk factors and consequences of brain changes on MRI in patients with symptomatic atherosclerotic disease. *Setting*: Hospital; persons newly referred to the UMCU for treatment of manifest atherosclerotic disease *Start*: 2001 *Number of participants*: 1309 *Data collection*: Clinical and cognitive data, psychosocial data, plasma markers, MRI, DNA *Follow-up*: Every 5 years

VUmc-AC: Amsterdam UMC, location VUmc; VUmc-APH: VUmc, Amsterdam Public Health research institute; RIVM: Rijksinstituut voor Volksgezondheid en Milieu; MUMC-IG: Maastricht UMC + Interne Geneeskunde; UMCU: Universitair Medisch Centrum Utrecht; EMC: Erasmus MC; LUMC: Leids Universitair Medisch Centrum; UMCG: Universitair Medisch Centrum Groningen; SCI: subjective cognitive impairment; MCI: Mild Cognitive Impairment. MRI: Magnetic Resonance Imaging; EEG: Electroencephalogram; CSF: cerebral spinal fluid; AD: Alzheimer's Disease; PET: Positron Emission Photography

Cohort enrichment with plasma biomarkers of vascular pathology and Alzheimer's disease pathology

Associations studied within NCDC are visualized in Fig. 1. As part of NCDC, cohorts sent previously collected blood samples to the Amsterdam UMC, location VUmc laboratory for analysis of plasma AD biomarkers (i.e., amyloid-beta ($A\beta_{1-40}$;$A\beta_{1-42}$), glial fibrillary acidic protein (GFAP), neurofilament light (Nfl) and p-tau 181); endothelial plasma biomarkers (i.e., soluble E-selectine, Vascular Cell Adhesion Molecule-1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1)), and inflammation plasma markers (i.e. Interleukin 6 (IL6), C-reactive protein (CRP), Serum Amyloid A (SAA), Interleukin 8 (IL8), Interleukin-1b (IL-1b), and Tumor Necrosis Factor α (TNF- α)). Centralized analysis of plasma markers minimized assay and batch variation as the majority of samples could be analyzed using the same assay and in the same batch. For those cohorts in which plasma AD biomarkers had previously been assessed with a different assay or in a different batch, bridging factors were calculated so that pooled analyses could be performed across cohorts. Efforts will be made to develop and share procedures and guidelines for pooled analysis of plasma biomarker data.

The public health impact of established risk factors for dementia

Findings from the scientific work packages will be integrated by performing mediation and population attributable fraction analysis. This knowledge will be leveraged to quantify the societal burden of dementia, optimize preventive trial design and its target population, and inform public health policy priorities for dementia risk reduction. Expected output includes policy documents regarding the societal burden of dementia and recommendations for population-wide and individual-level interventions for dementia risk reduction.

Knowledge dissemination

Dissemination of knowledge takes place through presentations and publications. Communication strategies have been developed to increase visibility of NCDC as a whole, and include dedicated websites [15, 16] and use of networks formed by other large national and international consortia such as the A personalized medicine approach for Alzheimer's Disease (ABOARD) project. Impact is realized through collaboration with other large (inter) national dementia research projects such as ABOARD, the Broadening Insight in Reduction of Dementia risk in the Netherlands (BIRD-NL) consortium, the Netherlands Cohort Consortium (NCC) and the Innovative Medicines Initiative European Platform for Neurodegenerative Diseases (IMI EPND) and involvement of NCDC -or its members- in new initiatives and consortia including a

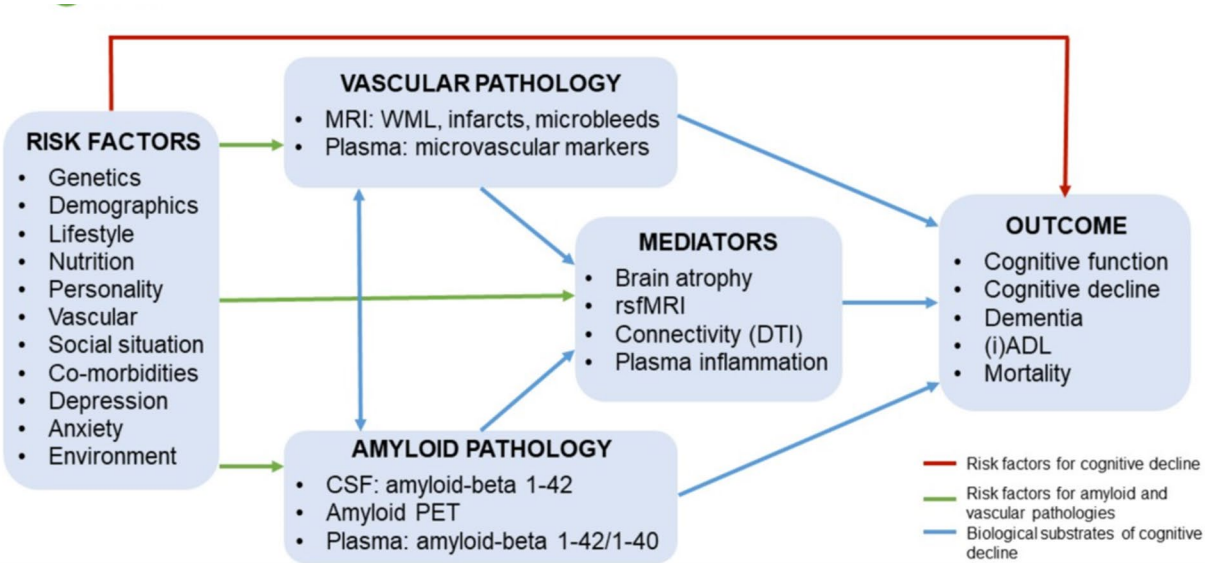

Fig. 1 Associations studied within in the Netherlands Consortium of Dementia Cohorts

nationwide collaboration to improve impact of dementia research, 'DEMentie en imPACT' (DEMPACT). The User Committee plays an important role in these processes, providing guidance and support. An important aspect of knowledge dissemination within the NCDC project is the education of its early-career researchers. To this end, we organize monthly calls and periodic educational sessions including a yearly NCDC winter school.

Results

Findability

The nine cohorts included have provided meta-data in the EPND catalogue at discover.epnd.org. EPND is a growing European network that aims to enable discovery of samples and data from studies on neurodegeneration [17].

Interoperability

To ensure consistent operationalization of variables in analyses using (pooled) NCDC data, we have developed harmonization scripts for all variables included in the NCDC minimal dataset. These scripts will be made available through the NCDC GitHub repository [18]. As harmonization of cognitive data can be especially challenging, and optimal operationalization is often dependent on context of use, we developed a cognitive data harmonization manual which can be utilized by any researcher working with cognitive data (Appendix II).

Accessibility & reusability

Medical imaging repositories

As part of the efforts to increase accessibility and reusability of data and harmonize data access procedures across cohorts, medical imaging repositories for scan management have been implemented and connected across cohorts. We used medical imaging repositories based on the XNAT software [19].

Personal health train infrastructure

One PHT use case has been successfully executed, providing a proof of concept, and a second use case is planned. In the first use case [20], a federated analysis approach was used to study the association between metabolic and brain age across data from The Maastricht Study, the LLS and the Rotterdam Study. Brain age was estimated based on structural brain MRI scans using a federated artificial intelligence model. In the second use case, we will examine associations of plasma markers of amyloid, tau and neurodegeneration with cognitive decline.

The contribution of vascular pathology and Alzheimer's disease pathology to the development of dementia

Multiple studies have been published in the context of NCDC. Supplemental Table 2 provides an overview of the objectives of these studies. Supplemental Table 3 provides an overview of the total number of plasma samples available per cohort. It should be noted that heterogeneity introduced by pooling of data across cohorts is an important limitation of multi-cohort analyses and potential cohort effects should be properly accounted for when working with NCDC data.

Discussion

The aim of NCDC is to enhance data infrastructure and improve the understanding of the etiology of dementia and the public health impact of established risk factors through joint analyses. The work done as part of NCDC

so far has resulted in improved findability, accessibility, interoperability and reusability of cohort data, as well as (scientific) output and expertise relevant to various stakeholder groups.

Lessons learned

Throughout the project, several barriers and facilitators to the improvement of the findability, accessibility, interoperability and reusability (FAIR) status of data and the establishment of frameworks needed for pooled and federated analysis have been identified. Facilitators include a dedicated legal professional that can initiate and oversee the establishment of the necessary ethical and legal frameworks, dedicated scientific and IT staff or contact persons at each study site and the availability and collation of expertise and knowledge across study sites. The largest barrier identified was the long time needed to establish the ethical and legal frameworks for data sharing. For the PHT infrastructure specifically, barriers included great variability in the availability of software and hardware tools across sites. We note that the establishment of PHT infrastructure requires a high short-term investment in terms of time and expertise. As its benefits become more evident in the long term, this may complicate the process of establishing support for its implementation and continuation. We also experienced that appointment of scientific personnel with affiliations at multiple sites could be both a barrier and facilitator, and this is something that should be considered carefully in new initiatives.

The lessons learned within NCDC can inform the design of future collaborative efforts and the formation of new consortia. Furthermore, the infrastructure and collaborations established within the NCDC framework also directly benefit other consortia such as NCC, which make use of data from the cohorts involved in NCDC. Lastly, the scientific work performed within NCDC has contributed to our understanding of the etiology of dementia and can provide building blocks for new scientific collaborations such as for BIRD-NL.

Future perspectives

NCDC has received additional funding from ZonMw (2024–2027) to assess p-tau 217, currently the most sensitive blood-based biomarker to track early, Alzheimer's Disease-related cognitive decline [21], in longitudinally collected plasma samples of all NCDC cohorts. Central assessment of this novel biomarker will be performed at the Amsterdam UMC, location VUmc lab, again to help minimize assay and batch variability and enable pooled analysis across NCDC cohorts.

NCDC is focused on increasing diversity by including the HELIUS study [22], a prospective cohort study on health and health care among an urban multi-ethnic population, in the consortium network. HELIUS includes participants of Dutch, African Surinamese, South Asian Surinamese, Ghanaian, Turkish and Moroccan origin. NCDC will also utilize the available statistical power to consider subgroup effects based on sex, socio-economic status and ethnic background.

Abbreviations

ABOARD	A personalized medicine approach for Alzheimer's disease
ADC	Amsterdam dementia cohort
BIRD-NL	Broadening insight in reduction of dementia risk in the Netherlands
CDM	Common data model
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DCS	Doetinchem cohort study
DEMPACT	Dementie en impact
EMIF-AD	European medical information framework for Alzheimer's disease
FAIR	Findable, accessible, interoperable, reusable
GFAP	Glial fibrillary acidic protein
Health-RI	Dutch health research infrastructure
ICAM-1	Intercellular adhesion molecule-1
IL-1b	Interleukin-1b
IL6	Interleukin 6
IL8	Interleukin 8
IMI EPND	The innovative medicines initiative European platform for neurodegenerative diseases
JCA	Joint controllership agreement
LASA	Longitudinal aging study Amsterdam
LLS	Leiden longevity study
NCC	Netherlands cohort consortium
NCDC	The Netherlands consortium of dementia cohorts
NFL	Neurofilament light
OMOP	Observational medical outcomes partnership
PET	Positron emission imaging
PHT	Personal health train
SAA	Serum amyloid A
SMART-MR	Second manifestations of ARTerial disease-magnetic resonance
TNF-α	Tumor Necrosis Factor α
VCAM-1	Vascular cell adhesion molecule-1
ZonMw	Netherlands organisation for health research and development

Supplementary Information

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Supplementary Material 1

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Author contributions

JEO, JEM, SV, WJJ and PJV drafted the main manuscript text. MB, PM, PPD, WMF, MIG, MAH, MAI, MTS, PES, WMMV, MB, IB, MB, EEB, AD, IF, SJFG, EJ, AALK, SM, LM, EPMC, ER, CGS, TTS, CET, ELT, IMWV, JMJV, MPHW and FJW reviewed and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are not publicly available due to ethical constraints but researchers interested in joining the NCDC consortium or working with the NCDC data are invited to contact the project leads (PJV and MAI) to discuss options for data access.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
TVS has received research operating funds from the Dutch Diabetes Foundation (fellowship grant number 2021.81.004) and the European Foundation for the Study of Diabetes." IV received funding from Health~Holland for a collaborative research project with Olink, Quanterix and Utrecht University. IV received speaker honoraria from Quanterix, paid directly to her institution. No other competing interests were declared.

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