Early detection of cognitive impairment in primary care: a mixed-methods protocol integrating data from multiple sources (DENDRITE study)

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SHORT TITLE: Early detection of cognitive impairment in primary care (DENDRITE)

Ángeles Almeida Parra[1,2¶], Andrea Ropero-Sánchez[3,4¶], Javier Zamora Romero[5], Laura Docío-Fernández[6], Mar Fatjó-Vilas Mestre[7,8,9], Susana Campuzano Ruiz[10], Pilar Lozano González[3,11], Olatz Alonso-del-Cura[3,11], Ana Montero Calle[12], Rodrigo Barderas Manchado[12,11], María Teresa Moreno-Casbas[3,11*], on behalf of the MedPer_DC Project Working Group[^]

[1]IBFG (Institute of Functional Biology and Genomics, CSIC, University of Salamanca), Salamanca, Castilla y León, Spain

[2]IBSAL (Institute for Biomedical Research of Salamanca, University Hospital of Salamanca, University of Salamanca, CSIC), Salamanca, Castilla y León, Spain

[3]Nursing and Healthcare Research Unit (Investén-isciii), Carlos III Health Institute (ISCIII), Madrid, Comunidad de Madrid, Spain

[4]University of Vic - Central University of Catalonia (UVic-UCC), Barcelona, Cataluña, Spain

[5]Biomedical Research Networking Centre for Epidemiology and Public Health (CIBERESP), Madrid, Comunidad de Madrid, Spain

[6]University of Vigo (UVigo), Pontevedra, Galicia, Spain

[7]FIDMAG Research Foundation, Barcelona, Cataluña, Spain

[8]Biomedical Research Networking Centre for Mental Health (CIBERSAM), Madrid, Comunidad de Madrid, Spain

[9]Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Facultat de Biologia, University of Barcelona (UB), Barcelona, Cataluña, Spain

[10]Complutense University of Madrid (UCM), Madrid, Comunidad de Madrid, Spain

[11]Biomedical Research Networking Centre for Frailty and Ageing (CIBERFES), Madrid, Comunidad de Madrid, Spain

[12]Chronic Disease Programme (UFIEC), Carlos III Health Institute (ISCIII), Madrid, Comunidad de Madrid, Spain

***Correspondence:**

Corresponding Author

mmoreno@isciii.es (MTMC)

[¶]These authors contributed equally to this work.

[^]Membership of the MedPer_DC Project Working Group is provided in the Acknowledgments.

Keywords: cognitive dysfunction, early diagnosis, Primary Health Care, predictive model, precision medicine.

Abstract

Globally, over half of cognitive impairment cases identified in population-based studies remain undetected, and up to 90% of mild cases go undiagnosed. This represents a major public health challenge with significant implications for ageing populations and health systems.

The present protocol outlines the integration of clinical, multiomic, healthcare, social, environmental, voice, and behavioral data, using artificial intelligence and advance statistical modeling, to develop a predictive risk model for the preclinical detection of cognitive impairment in adults aged 55–70 years.

This is an observational, multicenter, non-interventional study employing a convergent mixed-methods approach. The design combines a prospective quantitative phase with a qualitative one based on discussion groups.

The study will be conducted across six Spanish regions and seven primary healthcare centers located in different geographic areas. Each center will recruit 150 cognitively unimpaired participants, resulting in a total sample of 1050 participants. In addition, a calibration group of 100 participants diagnosed with mild cognitive impairment will be included.

This protocol has been developed in accordance with the STROBE guidelines to ensure methodological rigor, transparency, and reproducibility.

This research aims to develop a simple, cost-effective, and actionable tool for early preclinical detection of individuals at risk of cognitive impairment, enabling its integration into primary care and supporting timely, targeted interventions. This approach has the potential to reduce diagnostic delays, optimize healthcare resources, and promote equitable access to timely interventions, ultimately improving population health and quality of life.

Introduction and background

According to Reisberg's proposal in 1988, mild cognitive impairment (MCI) is defined as a decline in cognitive capacity that does not reach the threshold of dementia but occurs in the early phases of Alzheimer's disease [1]. Petersen (1999) further described it as a syndrome characterized by a loss of cognitive abilities beyond what is expected for an individual's age and educational background, though not severe enough to constitute dementia. Petersen and colleagues initially proposed that MCI primarily affects memory, without considering other higher mental functions [2].

In 2005, the concept of MCI was first discussed in the *International Conference on Prevention of Dementia* [3], and its definition was later expanded to acknowledge that it could affect cognitive domains beyond memory [4].

In 2024, the *Mayo Clinic* redefined MCI as the stage between the anticipated decline in memory, language, judgment, and other cognitive abilities associated with normal aging and the more severe deterioration observed in dementia [5]. This impairment can involve one or more cognitive domains, with memory being the most commonly affected in individuals who later progress to Alzheimer's disease. Functional limitations are usually mild and tend to affect complex tasks, while basic activities of daily living remain preserved. Individuals with MCI are often aware of their cognitive decline, and relatives may also notice these changes. Several studies have reported that MCI is associated with a reduced quality of life, increased stress and anxiety, and a higher incidence of depression [6].

Cognitive dysfunction carries significant socioeconomic consequences. It is associated with a threefold increase in hospitalizations, loss of independent living, and reduced productivity, generating a substantial financial burden for healthcare system and informal caregivers. In 2018, global costs were estimated to exceed one trillion US dollars [7]. Therefore, maintaining brain health throughout

adulthood, even in the presence of age-related cognitive changes, should be considered a strategic goal for healthcare systems.

The *Comprehensive Alzheimer's and Other Dementias Plan* reports that more than 50% of cognitive impairment cases identified in population-based studies remain undetected, and up to 90% of MCI cases go undiagnosed [8]. In Spain, the prevalence of MCI among individuals aged >50 years is estimated at 9.6%, with higher rates observed among older adults and women [9].

Risk factors associated with MCI in the 50–64 age group include depression, obesity, and cardiovascular disease [9], as well as lifestyle-related determinants such as diet, physical activity, social engagement, and stress. According to the *Precision Aging Model*, key risk categories include cardiovascular dysfunction, glucose disturbances, and chronic stress, along with emerging contributors such as immune dysregulation and circadian disruption [10]. Other associated factors include rural residence, lower educational attainment, and smoking [11]. Genetic variants can also modulate the impact of these risks, exacerbating or mitigating susceptibility to MCI.

Although these factors have been extensively studied, each explains only a portion of the variance and often applies only to specific subgroups. Few studies have integrated multiple biological, clinical, environmental, and behavioral determinants to better understand their combined contribution. A more comprehensive understanding of these interacting risk factors is essential for developing personalized preventive strategies.

Clinical management of cognitive disorders is shifting from a generalized clinicopathological approach toward precision personalized medicine (PerMed), which considers molecular alterations and individual biological variability. PerMed not only promotes patient-centered care and self-management but also enables more efficient resource utilization and potential cost savings. MCI exemplifies the

need for this approach, as it involves numerous genetic, protein-related, and neurobiological mechanisms.

There is an increasing need to implement robust PerMed programs that integrate clinical, multiomic, healthcare, social, environmental, voice, and behavioral data to improve the diagnosis, monitoring, and treatment of MCI in Spain. The *Global Advisory Group on Future MCI Care Pathways* has emphasized the importance of adopting technological tools and artificial intelligence (AI) to integrate these datasets and facilitate early detection [12].

Building on these priorities, this study seeks to integrate clinical, multiomic, healthcare, social, environmental, voice, and behavioral information using advanced analytical approaches, including AI. The primary goal is to bridge the gap between primary care and specialized neurology services by developing a practical and feasible screening tool that allows primary care health professionals to identify individuals at increased risk of MCI at an earlier stage, thereby supporting timely referral, preventive action, and more equitable care pathways. By moving beyond reliance on the Mini-Mental State Examination (MMSE) as the sole screening instrument, this approach aims to reduce diagnostic delays, optimize resource allocation, and improve real-world care pathway for at-risk patients. Central to achieving these objectives, the study focuses on developing a predictive model to assess MCI risk and support earlier, personalized interventions, integrating accessible data sources into a comprehensive framework to enhance early detection and inform clinical decision-making in primary care.

Objectives

General objective

This study aims to integrate clinical, genetic, molecular, proteomic, healthcare, social, environmental, voice, and behavioral data, using AI-based analytical techniques and statistical models, to develop a predictive risk model for the preclinical detection of cognitive impairment in adults aged 55–70 years. By enabling early identification, the model seeks to support the effective implementation of PerMed approaches for cognitive impairment in primary care. This protocol outlines the study design and methodology.

Specific objectives

1. Identify factors associated with MCI in adults aged 55-70 without a cognitive impairment diagnosis, with particular emphasis on factors systematically documented in primary care health records and those collected at the point of care via biosensors.
2. Analyze the influence of social context, lifestyle habits, and health behaviors on the onset of MCI in adults aged 55–70 without a cognitive impairment diagnosis.
3. Validate voice analysis, including both acoustic and linguistic features, as a non-invasive and ecological biomarker of cognitive impairment.
4. Explore the experiences, perceptions, and social risk awareness of adults aged 55–70 regarding MCI and dementia and examine their relationship with social determinants of health.
5. Validate genetic and proteomic markers (including autoantibodies and proteins) as preclinical markers of neurodegeneration and Alzheimer's disease using organoids, peripheral blood mononuclear cells (PBMCs), and plasma samples.
6. Integrate multi-source data for early detection of MCI using AI-based and statistical analyses to synthesize clinical, genetic, molecular, behavioral, and voice profiles.

Materials and methods

Setting

The study will be conducted in primary healthcare centers across seven locations in Spain: Albacete, Alicante, Barcelona, Bilbao, Huelva, Lleida, and Madrid. These centers represent both urban and rural settings and provide general primary care services to a diverse patient population. The selected locations were chosen to capture geographic, demographic, and socioeconomic variability across the country.

Design

This is an observational, multicenter, non-interventional study using a convergent mixed-methods design. The study combines a prospective quantitative phase with a qualitative phase involving discussion groups, allowing integration of numerical data and participant perspectives to comprehensively address the research objectives. This design allows quantitative data to be complemented by qualitative insights from discussion groups, ensuring that the model not only identifies statistical predictors but also reflects patient and community perspectives.

Sampling and recruitment

The study sample consists of a cohort of 1050 non-institutionalized participants, aged 55–70 years, affiliated with primary care centers in the study locations, with a documented medical record within the last 12 months, and without an established cognitive impairment diagnosis (MMSE >24). In addition, a calibration group of approximately 100 individuals with a confirmed diagnosis of MCI will be included to validate voice analysis procedures and genetic and proteomic markers. Given the limited availability of participants aged 55–70 with MCI, recruitment for this group will be conducted via

consecutive sampling of medical records. This calibration group is expected to represent approximately 15% of the overall cohort sample.

The MMSE has been selected as the primary cognitive screening tool for inclusion and exclusion criteria due to its widespread adoption in Spanish primary care, its entrenched use in clinical guidelines, seamless integration into Electronic Health Records, and familiarity among healthcare providers. To enhance diagnostic robustness, MMSE results will be combined with four additional cognitive tests and other easily obtainable clinical and functional variables. In cases of substantial discrepancies between scores, a clinical adjudication committee will review individual data to ensure diagnostic consistency [13,14].

Participants of the cohort will be selected from randomized lists of eligible patients at each primary care center, with stratification by age (5-year intervals) and sex. Each center will recruit approximately 150 participants. Exclusion criteria include significant difficulty completing self-reported questionnaires, underlying health or genetic conditions that may affect biological analyses, and institutionalization during follow-up. Cohort participants will undergo assessments at baseline and after 16 months to evaluate changes over time. For the qualitative phase, discussion groups will be formed using a purposive sample drawn from cohort participants, ensuring representation from urban and rural settings as well as less-advantaged areas.

As no previous studies have integrated the range of data sources used here, and the main analyses will employ advanced processing techniques, the chosen sample size ensures adequate events-per-variable ratio for predictive modeling while balancing feasibility across multiple centers. Based on conservative estimates, 80–85% of the initial cohort is expected to complete the 16-month follow-up, resulting in 800–850 participants. With an estimated 15% prevalence of MCI, approximately 158 events are

anticipated, sufficient to explore up to 15 variables in accordance with empirical guidelines recommending 10–20 events per predictor to minimize overfitting [15].

In summary, the proposed sample balances feasibility and methodological rigor for this initial development phase, providing a solid foundation for future refinement and broader implementation.

Data collection

Data will be collected during participant visits to their primary care centers and through mobile and digital monitoring. The main data domains include:

A. Clinical and sociodemographic data

- **Clinical data**: active International Classification of Primary Care (ICPC) codes and active pharmacological prescriptions in the last 24 months for hyperlipidemia, hypertension, diabetes, cardiovascular, and cerebrovascular disease.
- **Contextual factors**: place of residence (rural/urban), educational level, marital status, occupation, socioeconomic status, and level of contribution to medication costs.
- **Lifestyle habits**: tobacco, alcohol, and other substance use; exercise and nutritional habits, and sleep quality and patterns.
- **Cognitive assesments**: Memory Alteration Test (M@T), Montreal Cognitive Assessment (MoCA), MMSE, and complementary tests (Fototest and MiniCog©) for integration into IMPaCT Predictive Medicine.
- **Self-reported health perception:** EQ-5D-5L.

B. Point-of-care clinical assessments

– **Gait speed**: time to cover 4 meters, expressed in meters per second. It will also be assessed under challenging conditions, such as performing a secondary task, using the Walking While Talking test, which provides greater sensitivity to early functional and preclinical cognitive changes.

– **Speech fluency and content**: acoustic analysis will be performed on recorded speech from memory tests, image descriptions, and free-text responses. Automated speech recognition and natural language processing algorithms will be used to extract linguistic and paralinguistic features and compute relevant statistics.

C. Genetic, molecular and proteomic data

– **Omic analysis:** genome-wide genotyping will be performed to estimate polygenic risk scores (PRS) for cognitive decline using established GWAS data. Standard quality control and imputation procedures will be applied to ensure data robustness. Proteomic analyses will focus on identifying dysregulated proteins associated with MCI and Alzheimer's disease through quantitative profiling. Selected genomic and proteomic markers will be validated in plasma and PBMCs using complementary assays such as PCR and immunodetection. These analyses aim to provide biological indicators that, when integrated with clinical and behavioural data, may enhance early risk prediction in primary care.

– **Liquid biopsy:** a liquid biopsy approach will be used to validate a panel of previously reported protein markers of Alzheimer's disease and to explore novel candidates for early cognitive decline. This includes the development of a biosensing platform capable of integrating multiple markers (genetic variants, PRS, and proteins) into a single test. Blood samples (10 ml) will be collected at baseline and follow-up from all participants. A subset of individuals with the highest and lowest cognitive scores will undergo more detailed proteomic and liquid biopsy analyses. In addition, organoid models derived from control and Alzheimer's disease samples will support the validation of promising biomarkers, bridging laboratory discoveries with clinical application.

D. Behavioral and social interaction data

Data will be collected via the eB2 MindCare mobile application:

I. Active Monitoring:

– **Social support network.** The Arizona Social Support Interview Schedule (ASSIS) will be used to elicit networks related to material support, physical assistance, intimate interaction, guidance, feedback, and positive social interactions [16]. The Social Support Questionnaire (SSQ6-SF) assesses the number of people the participant perceives as providing support across six different areas, along with their overall satisfaction with the support received in each area [17].
– **Individual and social interactions skills**. Various theoretical game scenarios (the prisoner's dilemma, trust game, investor game, risk aversion, and dictator game) will be used to elicit how participants interact with each other [18]. This assesses the formation and stability of social connections and individual skills, with an emphasis on cognitive reflection tests and other related aspects (arithmetic, impatience, and so on). The procedures developed by Brañas-Garza et al. (2019) will be used [19].

II. Passive Monitoring:

– **Physical activity:** distinguishes the following types of activities performed throughout the day: still, standing, walking, running, cycling, and using transportation.
– **Steps:** periodically will record the number of steps detected by the phone's pedometer.
– **Actigraphy:** periodically will calculate the actigraphy signal using the device's accelerometer.
– **Sleep patterns:** will calculate the sleep time based on actigraphy signals and light records daily.
– **Mobility:** location data will be collected to determine the amount of time participants spend at home versus outside the home.

– **Phone application usage:** will record the time spent by the participant using installed applications.

E. Discussion groups

One discussion group per location will explore social perceptions of cognitive impairment risk. Discussion groups emphasize group dynamics, aiming to produce a collective discourse through group conversations. This technique involves selecting samples based on structural segmentation criteria combined with specific and operational criteria related to the research object. Groups will meet in community settings outside primary care centers, follow a guide developed with researchers and Patient and Public Involvement (PPI) representatives, last approximately two hours, and be audio-recorded for analysis [20].

Data management

Data will be collected electronically by project researchers using Research Electronic Data Capture (REDCap). Quality control measures, including internal monitoring and weekly reporting, will be implemented to ensure timely error correction and optimize data integrity. Digital data will be accessible only to the research team through a password-protected server.

Genomic and proteomic data will be processed in independent laboratories in Spain following standardized protocols. Biosensing platforms and liquid biopsy analyses will be conducted at a university-based research facility. Voice analysis and passive data collection from mobile applications will be performed by computational research groups, while biostatistical analyses will be carried out by a clinical biostatistics unit. Qualitative variable analyses will be conducted by university research units specializing in nursing, healthcare, and healthy aging.

Data analysis

This study follows the PROGRESS framework, which provides methodological guidance for research aimed at identifying predictors and developing predictive models [21]. A detailed statistical analysis plan will be finalized before database lock and prior to performing the main analyses. This plan will integrate advanced methodologies from multiple disciplines, including bioinformatics, statistics, and probabilistic modeling, to construct a comprehensive profile of clinical, multiomic, healthcare, social, environmental, vocal, and behavioral features associated with MCI.

An initial analysis will be performed using a training dataset composed of two homogeneous subgroups: participants from the cohort with the highest cognitive performance (considered cognitively healthy) and participants from the calibration group with the lowest cognitive performance (diagnosed with MCI). This approach aims to explore the most discriminative features across domains. All research teams involved in the different analytical domains will use the same training dataset to minimize the risk of overfitting. To ensure robustness and generalizability, bootstrapping techniques and internal validation procedures will be applied. In a subsequent phase, the predictive performance of the identified features and models will be tested on the remaining dataset. The final predictive risk model will integrate the variables with the highest discriminative potential, prioritizing the principle of parsimony, interpretability, and clinical applicability in primary care.

The qualitative phase will complement the quantitative analysis and will follow Braun and Clarke's (2013) reflexive thematic analysis framework [22]. Audio-recorded discussion groups will be transcribed verbatim, and analysis will begin after the first group session using an inductive approach, proceeding in parallel with data collection. All research team members will review the transcripts to gain familiarity with participant's account, identify meaning units, and collaboratively develop initial codes. Through an iterative refinement process, codes will be reorganized into broader categories and structured into a thematic map encompassing main themes and subthemes. Relevant verbatim

quotations will support the interpretation of findings, ensuring that participants' perspectives are accurately represented.

To guarantee scientific rigor and reproducibility, this study will follow internationally recognized reporting standards. The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement, will guide the reporting of the predictive modeling process [23], while the Consolidated Criteria for Reporting Qualitative Research (COREQ) be followed for the qualitative phase [24]. By integrating these methodological frameworks and adhering to established guidelines, the study aims to deliver results that are both scientifically robust and clinically meaningful.

Ethical considerations

Researchers will ensure full compliance with all applicable legal, regulatory, and administrative provisions related to the ethical aspects of this study. Formal approval has been obtained from the corresponding Clinical Research Ethics Committees prior to participant recruitment. All study procedures will be conducted in accordance with the principles outlined in the Nuremberg Code, the Declaration of Helsinki, relevant international guidelines, applicable national legislation, and Good Clinical Practice (GCP) standards.

Prior to participation, all individuals aged 55–70 years will be required to provide written informed consent. Trained research staff, qualified in human subject protection and GCP, will conduct the consent process in a private setting after confirming each participant's eligibility and ensuring their full understanding of the study's objectives, procedures, potential risks, and anticipated benefits. For the cohort group, which will consist of cognitively healthy individuals without a diagnosis of MCI, the research staff will provide all information and address any questions before obtaining consent. For the

calibration group, participants will present with MCI; however, by definition, their cognitive alterations will not reach a level that compromises their ability to understand the information provided. In these cases, the language used during the explanation will be adapted as needed, and additional clarifications will be given to ensure comprehension. If there is any doubt that a participant has not fully understood the study or the consent form, and therefore is not providing free and informed consent, this will be considered a reason for exclusion from the study. This consent procedure, including the assessment of participants' capacity to provide consent, has already been reviewed and approved by the corresponding ethics committees. Two signed copies of the informed consent document will be obtained: one retained by the participant and the other securely stored in the registry of the corresponding primary healthcare center.

Regarding the risk communication strategy, and in strict adherence to the approved ethical protocol and informed consent agreements, we emphasize that no participant with suspected cognitive impairment will remain without a definitive diagnostic confirmation or exclusion by a neurologist. If clinically relevant anomalies are detected during cognitive screening, the participant's primary care physician will promptly communicate all findings to the patient to ensure continuity within their trusted care relationship. The physician will then coordinate an immediate referral to a neurologist for comprehensive evaluation. Subsequently, the physician will oversee the diagnostic process, manage follow-up care, and monitor long-term outcomes, guaranteeing seamless integration of specialized expertise into the existing therapeutic alliance.

The consortium will guarantee confidentiality and anonymity throughout the study. All participant data will be pseudonymized and stored on secure, password-protected servers, accessible only to authorized study personnel. Data management will comply with applicable Data Protection Legislation, including the General Data Protection Regulation (GDPR), where relevant.

Finally, adherence to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines reflects our commitment to transparency, reproducibility, and accountability in reporting the study findings [25]. The complete STROBE checklist is provided in Supplementary File S1.

Limitations

This study has several limitations that should be considered when interpreting the results. Its observational design precludes causal inference, and associations between predictors and cognitive impairment should be interpreted as associative rather than causal. The study population is limited to non-institutionalized adults aged 55–70 years affiliated with primary care centers, which may introduce selection bias and limit generalizability to other age groups, institutionalized populations, or regions with different healthcare access.

Although the MMSE is the most widely used cognitive screening tool in Spanish primary care and facilitates integration with existing clinical workflows, it has limited sensitivity and specificity for detecting early-stage MCI [13,14]. This study does not aim to validate the MMSE but rather to leverage its ubiquity as a practical starting point. To address potential misclassification, we combined MMSE results with four complementary cognitive tests and other easily obtainable clinical and functional variables. Additionally, a clinical adjudication committee will review cases showing substantial discrepancies between scores, ensuring diagnostic consistency and minimizing classification bias.

While advanced multiomic, vocal, and behavioral analyses provide a rich dataset, technical variability and evolving analytic methods may affect reproducibility or external validation. The 16-month follow-up, although typical in older adult cohorts, may be relatively short to fully capture long-term cognitive changes, yet it helps minimize participant attrition. Inclusion of vulnerable populations affected by

social determinants of health remains challenging, and although efforts will be made to ensure their participation, these groups may be underrepresented.

Despite these limitations, the study incorporates careful sample stratification, standardized protocols, and internal validation to maximize methodological rigor. The findings are expected to provide a solid foundation for future research and support the development of early detection strategies for MCI in primary care settings.

Furthermore, as this is a development study, external validation in independent cohorts will be necessary before large-scale implementation. Therefore, the results should be considered preliminary, providing a foundation for future replication and adaptation within health systems.

Gender perspective

The project recognizes that women have a higher prevalence of cognitive impairment than men, with an estimated ratio of approximately 1.3:1, and will examine sex-specific effects on outcomes. Gender will be incorporated into the analysis of social behavior, considering that women generally have longer life expectancy and are at greater risk of social isolation and loneliness. Sex-dependent differences will also be evaluated in multiomic studies to identify biological markers that may vary between men and women. An inclusive approach will be adopted to address biological, social, and cultural factors, ensuring equitable research practices [26].

The project also emphasizes the promotion of women's participation and leadership in research. Currently, 73% of consortium researchers are women, with several holding key leadership roles. Measures are in place to maintain a non-discrimination policy, achieve gender balance in project activities, support fair hiring practices based on merit, and capabilities, and foster the advancement of women throughout the project’s execution.

Implications in practice

Through individual and combined analyses of the collected data, the study is expected to identify early indicators of MCI. These indicators will be integrated into a single predictive risk model for the preclinical detection of MCI in adults aged 55–70 years, with direct application in primary care. Designed for integration with electronic health records and other digital platforms, the model will provide general practitioners and nurses with a practical decision-support tool for risk stratification, patient counseling, and referral pathways.

This study is conducted within the framework of the IMPaCT infrastructure, a precision medicine platform organized three interconnected programs: cohort, data, and genomics. IMPaCT's mission is to generate and transfer the knowledge necessary to support the effective implementation of PerMed. The integration of predictive tools and multiomic data through this infrastructure is anticipated to facilitate a paradigm shift in healthcare, enabling more preventive, diagnostic, and personalized therapeutic approaches that improve effectiveness and safety for individual patients.

Early insight and discussion

The impact and usefulness of predictive models or individual markers of MCI are highly relevant in the context of an aging population and the rising incidence of neurodegenerative diseases.

A predictive model of cognitive impairment enables early identification of individuals at higher risk, allowing for timely preventive interventions such as lifestyle modifications, cognitive and social stimulation programs, and, where appropriate, pharmacological treatments. This early approach has the potential to delay disease progression and improve clinical outcomes. Additionally, a predictive model can support healthcare professionals in providing personalized care, optimizing resource

allocation, and promoting a more equitable distribution of healthcare services, ultimately improving patients' quality of life.

Individual markers of MCI, such as specific blood-based biomarkers or a neuropsychological measures, can also be highly valuable. These markers provide objective and quantifiable information about cognitive status, facilitating early diagnosis, monitoring disease progression and guiding treatment decisions. They are equally critical in clinical research, serving as outcome measures in clinical trials and supporting the evaluation of novel therapeutic interventions.

In practice, predictive models and individual markers are powerful tools that can significantly affect the prevention, diagnosis, treatment, and management of neurodegenerative conditions, advancing the implementation of PerMed in primary care.

An innovative aspect of this study involves discussion groups, to explore patient's preferences regarding the communication of results derived from predictive models or biomarkers. Respecting the right to information and non-information is a cornerstone of patient autonomy and the patient-provider relationship. While some individuals may wish to know their full risk profile, others may prefer limited information, particularly given the uncertainties of disease progression and the absence of curative treatments. Incorporating these preferences fosters trust, enhances patient satisfaction, and promotes patient-centered care.

Finally, by embedding this exploratory work within a national population-based framework, the study lays the foundation for future refinement and expansion toward more sophisticated predictive models as data maturity and funding opportunities evolve. This approach balances methodological rigor with real-world clinical applicability, aiming to bridge the current gap between primary care and specialized neurology services while advancing the implementation of precision medicine in cognitive health.

Progress to date and lessons learned

The first participant was recruited on 14/03/2024. Recruitment is expected to conclude by December 2025, with data analysis completed by June 2026. The study workflow has been standardized across participating centers:

1. Initial recruitment is conducted by the primary care physician, who provides study information, obtains informed consent, and records clinical and sociodemographic data.
2. Nurses administer cognitive screening tests, assist with the installation of the mobile application, and collect voice recordings.
3. A second visit includes gait speed testing and blood sample collection.

Blood sample handling varies between sites depending on available infrastructure. Some centers process samples locally, whereas others transport them to specialized biobanks. A standardized transportation circuit to analysis laboratories is currently under development.

An ongoing discussion within the research team, guided by the PPI group, concerns how and what study-related information should be returned to participants. Defining a clear policy on this matter is critical to align ethical obligations with patient expectations.

Finally, this project represents the first nationally funded initiative in Spain with shared leadership between biology and nursing. This interdisciplinary collaboration has proven highly enriching, fostering mutual learning and providing a more comprehensive perspective. Notably, nurses play a central role in almost all phases of the study, including coordination, recruitment, data collection, and participant engagement, demonstrating leadership within a multidisciplinary framework.

Conflict of interest

The authors declare that there are no commercial or financial relationships that could be perceived as a potential conflict of interest in relation to this research.

Acknowledgments

The authors wish to acknowledge the contributions of the MedPer_DC Project Working Group, comprising over 100 researchers from clinical, academic, and technical backgrounds. A complete list of members is provided in Supplementary File S2.

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528 Supporting information

529 Supplementary File S1. STROBE checklist.

530 Supplementary File S2. List of members of MedPer_DC Project Working Group.