Executive Summary

First reporting period (01/04/2024 – 31/03/2025)

Summary of the context and overall objectives of the project

Emerging evidence points at substantial comorbidity and shared genetics between adult Attention Deficit Hyperactivity Disorders (ADHD) and cardiometabolic diseases (i.e., Obesity, Type-2 Diabetes and cardiovascular disease). Inadequate treatment of cardiometabolic disease is strongly associated with premature death and substantial societal costs. National guidelines of cardiometabolic disease have stressed the importance of co-occurring psychiatric disorders. However, even though ADHD is a common (prevalence ≈2 to 5% in adults) and serious complex chronic condition, knowledge about appropriate management of adults with ADHD and co-occurring cardiometabolic disease is lacking.

The overall aim of TIMESPAN is to advance the management of adult (ADHD) and cooccurring cardiometabolic disease by improving the identification and treatment of individuals with these comorbidities. **Our specific objectives are:**

1) Determine if ADHD in adults worsens prognosis and hampers the management of cardiometabolic disease (WP1).
2) Identify the cardiometabolic risks and benefits of multidisciplinary treatment approaches in patients with ADHD (WP2, WP5).
3) Identify reasons for ADHD treatment discontinuity in adult patients with and without cardiometabolic disease. (WP3, WP4, WP5).
4) Identify patients with ADHD at high-risk for poor cardiometabolic outcomes and treatment discontinuity (WP6).
5) Provide an ethical strategy and (FAIR) data management plan (DMP) to allow for maximal transparency, open access/science, usability and reproducibility (WP7).
6) Broadly disseminate the TIMESPAN findings amongst stakeholders (from patients to health authorities) and provide guidelines for the clinical management of adults with ADHD and co-occurring cardiometabolic disease (WP8).
7) Train scientists, clinicians and a new generation of interdisciplinary researchers (WP8).

Work performed from the beginning of the project to the end of the period covered by the report and main results achieved so far

For objective 1, we have obtained data access for the register data and produced harmonized definitions. We have developed a common protocol and distributed network approach that allow us to perform cross-country pooling and comparisons. We have finalized or are working on several multisite/ country projects.

For objective 2, we have obtained data access for the register data and produced harmonized definitions for ADHD medication and the relevant outcomes (i.e., a common code book). We have developed a common protocol and distributed network approach that allow us to perform crosscountry pooling and comparisons. We are working on several projects and have protocols ready for several cross-country studies. We have acquired real-world data using novel Remote Measurement Technology (RMT) including both active (smartphone active app) and passive (smartphone passive app and a wearable device) monitoring to capture real-time disease processes that cannot be captured by register-based studies, including ongoing real-world data regarding detailed aspects of ADHD medication treatment, physical activity and cardiometabolic risks, over a 12-month monitoring period. Baseline assessments have been completed following the conclusion of participant recruitment (304 participants in total). We have published the protocol.

For objective 3, we have estimated the expected treatment length of each medication dispensation using a validated machine-learning algorithm, taking advantage of the free-text prescription and package information on the prescription. We have developed protocol and analysis plans for two cross-country studies: i) clinical modifiers of ADHD treatment discontinuity and ii) ADHD treatment discontinuity in adults with co-occurring cardiometabolic disease. We have also finalized our genomic project (WP4) to advance the understanding of the biological mechanisms underpinning ADHD treatment discontinuation. As described in objective 2, we have collected data that will allow us to identify predictors and correlates of adult ADHD medication treatment discontinuity with a focus on day-to-day reported side-effects, using RMT ADHD Remote Technology (ART).

For objective 4, we have developed the relevant machine learning and deep learning models and shared codes in public repositories. We are now applying these models in large scale real-world datasets, optimizing the model performance in these datasets and evaluating the generalizability to reserved unseen data, or datasets from different cohorts. Our goal is to develop generalizable risk stratification tools that will be especially useful in primary care settings where ADHD itself, well as its comorbidity with cardiometabolic disease is typically under-identified in adults.

For objective 5, we have formed an Ethics and Data Management board as well as a Data Management Advisory Committee. We also oversee adherence to all existing ethical and safety provisions and we have also developed and updated Data Management Plan (DMP). Furthermore, we have overseen all ethics approval documents for all sites involved in newly recruiting patients. In addition, we have also overseen the collection of all approvals from the existing cohorts that are used in TIMESPAN. We have also made great progress in overseeing, supervising and implementing our plan for preregistration, and the common protocols and distributed network approach.

For objective 6, many dissemination actions have been carried out towards scientists, the medical community (e.g. research articles, lectures at congresses, videos, infographics), patients and general audience (e.g. website, social media activities, infographics). We contributed to cross-project collaboration together with PRIME.

For objective 7, the TIMESPAN mentor mentee program, established in the previous reporting period, is well received and has identified and paired more Early Career Researchers with a TIMESPAN senior scientist as mentor during RP2. The ECRs developed personal portfolios specifying their personal training objectives and needs. We organized masterclasses for ECRs during our annual meetings. We created a training course in pharmacoepidemiological analyses using real-world data. We contributed to cross-project collaboration through active participation in the ECNP Course on Brain and Body.

Progress beyond the state of the art and expected potential impact (including the socio-economic impact and the wider societal implications of the action so far)

TIMESPAN is expected to improve the clinical outcomes, as well as quality of life in adult ADHD patients with co-occurring cardiometabolic disease and also to facilitate developments of new tools for advanced data management, monitoring and analytics for European stakeholders. TIMESPAN strategies to inform clinicians, patients, health authorities, and the general public allow for a sustainable implementation of our findings (e.g. recommendations for guidelines).

While most TIMESPAN projects are ongoing, we are already active in preparing to create societal impact. We have already published several important findings regarding the association between ADHD and cardiometabolic disease and about ADHD treatment discontinuity. Additionally, we are introducing the subject to the scientific community, patients, and the wider public, e.g. through webinars, symposia at congresses, and participation in activities of patient organisations.

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