Executive Summary

First reporting period (01/04/2021 – 30/09/2022)

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 started three projects in parallel about influence of ADHD on medication adherence of cardiometabolic disease (type 2 diabetes led by UMCG, hypertension led by KI and hyperlipidemia led by AU). We have developed a common protocol and distributed network approach that allow us to perform cross-country pooling and comparisons. We have already published several manuscripts.

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 cross-country pooling and comparisons. We are working on several projects and have protocols ready for 5 studies. We have also already published study findings. We have also prepared for a data collection that will acquire 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 unobtrusive, ongoing real-world data regarding detailed aspects of ADHD medication treatment, physical activity and cardiometabolic risks simultaneously, over a 12-month monitoring period.

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 a common protocol and distributed network approach that allow us to perform cross-country pooling and comparisons. We have also analysed common genetic variants and medication prescription data in 18,950 individuals with ADHD. Additionally, we have done preliminary Polygenic Risk Scores (PRS) analyses to test for potential

association between increased polygenic risk burden and medication discontinuation. As described in objective 2, we have prepared a data collection 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 overseen adherence to all existing ethical and safety provisions and we have also developed a Data Management Plan (DMP) and this DMP is still up to date. 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 the common protocols and distributed network approach together with our participating sites.

For objective 6, we have developed the TIMESPAN website and implemented social media channels. We released a project brochure with the relevant information of the project and also created a roll-up poster to increase the visibility of the project in international meetings where the project will be presented. During this period different manuscripts were submitted for publication as open access international journals (BMC psychiatrist, Neuroscience & Biobehavioral Reviews). We have published on systematic review/meta-analysis covering ADHD medication and cardiovascular diseases. We have also submitted two systematic reviews on ADHD and type 2 diabetes and cardiovascular diseases: “The association between type 2 diabetes and attention deficit/hyperactivity disorder: a systematic review, meta-analysis, and population-based sibling study” and “The associations between ADHD and cardiovascular diseases: a systematic review and meta-analysis”. The results of these papers will be part of the future recommendations and guidelines implemented by the project.

For objective 7, we have established a mentor mentee program within TIMESPAN. Each ECRs have a mentor (a senior academic) from another site within TIMESPAN. Mentors meet with their mentees as often as required, with at least one in-person meeting annually and additional on-line or telephone meetings. TIMESPAN ECRs developed personal portfolios specifying their personal training objectives and needs. We have organized a masterclass for ECRs during our annual meeting.

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 also facilitates developments of new technological tools for advanced data management, monitoring and analytics for European stakeholders. TIMESPAN strategies to inform clinicians, patients, health authorities, and general public allow for a sustainable implementation of our findings (e.g. recommendations for treatment guidelines).

While most TIMESPAN projects are ongoing, we are already active in preparing to create societal impact: In particular, we have already submitted three systematic reviews and meta-analysis and we are reviewing clinical guidelines for the management of cardiometabolic disease in ADHD. We have also already published several important findings regarding the association between ADHD and cardiometabolic disease. 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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