TIMESPAN

Management of chronic cardiometabolic disease and treatment discontinuity in adult ADHD patients

H2020 – 965381

D8.5.– Training course in pharmacoepidemiological analyses using realworld data for relevant stakeholders

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Workpackage leader	Tamara Berghammer (concentris)

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Abbreviations

ADHD	Attention deficit/hyperactivity disorder
CVD	Cardiovascular Diseases
DAG	Directed Acyclic Graphs
ECNP	European College of Neuropsychopharmacology
ECS	Early Career Scientist
RCTs	Randomized Controlled Trials
T2D	Type 2 Diabetes

Table of Contents

1. Executive Summary

This deliverable contains a detailed description of the TIMESPAN training course in pharmacoepidemiology, targeted towards researchers, particularly Early Career Scientists. We provide an overview of the course content and also provide detailed information about learning objectives as well as information about impact, including data from our evaluation.

We concluded that the TIMESPAN training course in pharmacoepidemiology successfully provided researchers, particularly Early Career Scientists, with essential knowledge and skills to analyse real-world data in the context of ADHD and cardiometabolic health. By covering key epidemiological and methodological principles, the course strengthened participants' ability to apply advanced pharmacoepidemiological approaches within their respective work packages.

We also think the course fostered interdisciplinary collaboration by engaging researchers across TIMESPAN, facilitating knowledge exchange between work packages, and contributing to broader scientific discussions through its integration into the ECNP Course on Body and Brain.

2. Deliverable report

2.1. Work performed as described in the Grant Agreement

Task 9: Training and mentorship of work package 8 describes the task at hand as follows: “We will organize a course in pharmaco-epidemiological analyses using real-world data for relevant stakeholders, including scientists linked to pharmaco-epidemiological networks across the world (e.g., the International Society of Pharmacovigilance).”

The training course is the result of a combination of TIMESPAN's internal efforts and collaborative initiatives. It features six concise 30-45-minute lectures, each designed to provide focused insights on key topics. A dedicated subpage on our website, accessible via this link https://timespan.eu/training-course-in-pharmacoepidemiology/, houses this training course, offering easy access to this resource.

2.1.1. Learning objectives

Upon completion of the training course, participants will be able to:

- Understand the foundational principles of pharmacoepidemiology and the use of big real-world data in psychiatric and cardiovascular research.
- Gain insights into advanced epidemiological methods, including how to address unmeasured confounding through family data analysis.
- Explore the epidemiological overlap between type 2 diabetes and brain disorders, and the clinical considerations for studying cardiovascular risks in ADHD.

2.1.2. Overview of the course

This training course offers a comprehensive introduction to pharmacoepidemiological analyses using real-world data, designed to equip relevant stakeholders with essential skills and knowledge. Through a series of expert-led masterclasses, participants will explore key concepts in pharmacoepidemiology and the application of big data in psychiatric and cardiovascular research. Topics include advanced methods for addressing unmeasured confounding using family data, the interplay between type 2 diabetes and brain disorders, and practical considerations for studying cardiovascular risk in ADHD using registry data. Together, these sessions provide a robust foundation for conducting impactful real-world data analyses in pharmacoepidemiology.

Nr.	Topic	Speaker(s)	Time
1	Pharmaco-epidemiology and big (real world) data	Prof. Dr. Henrik Larsson	30 minutes
2	What can family data tell us about unmeasured confounding?	Ralf Kuja-Halkola, PhD	35 minutes
3	Epidemiological conditions of cardiovascular diseases	Pontus Andell, MD, PhD	40 minutes
4	Psychiatric epidemiology using (big) real-world data: an overview of key principles	Prof. Dr. Henrik Larsson	30 minutes
5	Epidemiology of the overlap between Type 2 diabetes and brain disorders	Prof. Dr. Søren Dalsgaard	30 minutes
6	Studies of cardiovascular risk in ADHD using registers - Clinical and practical considerations	Prof. Dr. Henrik Larsson and Dr. Zheng Chang	40 minutes

2.1.3. Target audience

With the training course, we aim to reach scientists, in particular early career scientists within and outside TIMESPAN, who are interested in pharmacoepidemiological studies, real-world data, psychiatric research and evidence-based treatments for ADHD. Other target stakeholders are health care professionals, members of the scientific community, and experts in pharmacoepidemiology who would like to increase their knowledge about different types of ADHD epidemiology studies and ADHD pharmacoepidemiological studies.

2.1.4. Content of the lectures

Lecture 1: Pharmaco-epidemiology and big (real world) data – Prof. Dr. Henrik Larsson

Learning objectives:

- Understand the limitations of randomized controlled trials (RCTs) in studying ADHD medication, including challenges with sample sizes, follow-up durations, and studying rare or harmful outcomes.
- Learn how real-world data, including national registers, can complement RCTs by providing insights into both short- and long-term effects of ADHD medication.
- Explore the use of within-individual study designs to minimize confounding in pharmacoepidemiological research.
- Analyse key findings on the short-term benefits (e.g., reduced criminality and accidents) and risks (e.g., substance abuse and mania) associated with ADHD medication.

Main content:

- Overview of pharmacoepidemiology and the role of real-world data in ADHD research.
- Limitations of randomized controlled trials and how national registers complement them.
- Use of within-individual study designs to minimize confounding in pharmacoepidemiological research.
- Key findings on the short-term benefits and risks of ADHD medication, including reduced criminality and potential risks such as substance abuse.
- The importance of studying long-term effects of ADHD medication using big data.

Scientific reading material (open access):

- Chang Z et al. Risks and Benefits of Attention-Deficit/Hyperactivity Disorder Medication on Behavioral and Neuropsychiatric Outcomes: A Qualitative Review of Pharmacoepidemiology Studies Using Linked Prescription Databases. *Biol Psychiatry*. 2019 Sep 1;86(5):335-343.

Lecture 2: What can family data tell us about unmeasured confounding? – Ralf Kuja-Halkola, PhD

Learning objectives:

- Understand how family data can be used to address unmeasured confounding in epidemiological studies.
- Learn what directed acyclic graphs (DAGs) are and how they help visualize assumptions about causal relationships.
- Explore different study designs that leverage family-based comparisons to strengthen causal inference.

Main content:

- Introduction to confounding in epidemiological research.
- Explanation of family-based study designs and their advantages.
- Overview of DAGs as a tool for causal reasoning.
- Practical examples of how family data can reduce bias in observational studies.

Scientific reading material (open access):

- Linnet KM, Dalsgaard S, Obel C, Wisborg K, Henriksen TB, Rodriguez A, et al. Maternal lifestyle factors in pregnancy risk of attention deficit hyperactivity disorder and associated behaviors: review of the current evidence. *Am J Psychiatry*. 2003 Jun;160(6):1028-40.
- Thapar A, Fowler T, Rice F, Scourfield J, van den Bree M, Thomas H, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry.* 2003 Nov;160(11):1985-9.
- Skoglund C, Chen Q, D'Onofrio BM, Lichtenstein P, Larsson H. Familial confounding of the association between maternal smoking during pregnancy and ADHD in offspring. *J Child Psychol Psychiatry*. 2014 Jan;55(1):61-8.
- Kuja-Halkola R, D'Onofrio BM, Larsson H, Lichtenstein P. Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance. *Behav Genet*. 2014 Sep;44(5):456-67.

Scientific reading material (non open access):

- Capusan AJ, Kuja-Halkola R, Bendtsen P, Viding E, McCrory E, Marteinsdottir I, Larsson H. Childhood maltreatment and attention deficit hyperactivity disorder symptoms in adults: a large twin study. *Psychol Med*. 2016 Sep;46(12):2637-46.

Lecture 3: Epidemiological conditions of cardiovascular diseases – Pontus Andell, MD, PhD

Learning objectives:

- Understand the global burden and impact of cardiovascular diseases (CVD).
- Recognize the different types of CVD and their relevance in ADHD research.
- Learn how registry-based data is used to study CVD, including ICD codes, drug registries, and quality-of-care registries.
- Identify the strengths and limitations of registry-based research for cardiovascular epidemiology.
- Explore the interplay between CVD, mental health disorders (e.g., schizophrenia), ADHD, and the role of medication in cardiovascular outcomes.

Main content:

- What are epidemiological conditions of cardiovascular diseases?
- Registry-based research in CVD: The use of national registries, ICD codes, and prescription databases to study cardiovascular outcomes.
- Trends in CVD outcomes: Mortality and survival trends, the impact of medical advancements, and long-term risk assessment. What is the burden of cardiovascular diseases?
- CVD in Psychiatry & ADHD: Overlap between CVD and psychiatric conditions (e.g., schizophrenia), and potential cardiovascular risks associated with ADHD medication.

Scientific reading material (open access):

- Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study *BMJ* 2019;364:l223.
- Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, et al. Long-Term Progression and Outcomes With Aging in Patients With Lone Atrial Fibrillation *Circulation* 2007;115(24):3050-3056.
- Vinter N, Huang Q, Fenger-Grøn M, Frost L, Benjamin E J, Trinquart L et al. Trends in excess mortality associated with atrial fibrillation over 45 years (Framingham Heart Study): community based cohort study *BMJ* 2020;370:m2724.
- Tagalakis, Vicky et al. Incidence of and Mortality from Venous Thromboembolism in a Real-world Population: The Q-VTE Study Cohort *The American Journal of Medicine*, 2013;126(9):832.e13-832.e21.
- Torres-Acosta N, O'Keefe JH, O'Keefe CL, Lavie CJ Cardiovascular Effects of ADHD Therapies: JACC Review Topic of the Week, *Journal of the American College of Cardiology* 2020;76(7): 858-866.
- Andell P, Li X, Martinsson A, et al Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study *Heart* 2017;103:1696-1703.

Lecture 4: Psychiatric epidemiology using (big) real-world data: an overview of key principles – Prof. Dr. Henrik Larsson

Learning objectives:

- Participants will understand the types of research questions that can be addressed with psychiatric epidemiology research using real-world data.
- Participants will understand key principles for interpreting psychiatric epidemiology research using real-world data.
- Participants will learn about challenges and opportunities in prediction modelling studies using real-world data.
- Participants will learn about challenges and opportunities in pharmacoepidemiology studies using real-world data.

Main content:

- What is real-world data?
- Opportunities for psychiatric epidemiology: an overview of major research questions addressed with real-world data.
- Challenges in psychiatric epidemiology research.
- How to interpret psychiatric epidemiology research.

Scientific reading material (open access):

- Oliver D et al. Using Electronic Health Records to Facilitate Precision Psychiatry. *Biol Psychiatry*. 2024 Feb 24:S0006-3223(24)01107-7.
- Chang Z et al. Risks and Benefits of Attention-Deficit/Hyperactivity Disorder Medication on Behavioral and Neuropsychiatric Outcomes: A Qualitative Review of Pharmacoepidemiology Studies Using Linked Prescription Databases. *Biol Psychiatry*. 2019 Sep 1;86(5):335-343.

This lecture is part of the ECNP course on Body and Brain, organised in partnership with the PRIME, TIMESPAN, and CANDY consortia.

Lecture 5: Epidemiology of the overlap between Type 2 diabetes and brain disorders – Prof. Dr. Søren Dalsgaard

Learning objectives:

- Participants will understand the increased risk of psychiatric or neurological disorders in people with type 2 diabetes (T2D).
- Participants will learn about the increased risk of developing T2D in individuals with psychiatric or neurological disorders.

Main content:

- Longitudinal and cross-sectional studies of the overlap.
- Common risk factors for T2D and brain disorders.
- What comes first? Is timing important?
- Sex differences in the associations between T2D and brain disorders.

Scientific reading material (open access):

- Wimberley T, et al. Temporally ordered associations between type 2 diabetes and brain disorders - a Danish register-based cohort study. *BMC Psychiatry*. 2022 Aug 26;22(1):573.
- Kessing LV, Rytgaard HC, Ekstrøm CT, Knop FK, Berk M, Gerds TA. Antidiabetes Agents and Incident Depression: A Nationwide Population-Based Study. *Diabetes Care*. 2020 Dec;43(12):3050-3060.

This lecture is part of the ECNP course on Body and Brain, organised in partnership with the PRIME, TIMESPAN, and CANDY consortia.

Lecture 6: Studies of cardiovascular risk in ADHD using registers - Clinical and practical considerations – Prof. Dr. Henrik Larsson and Dr. Zheng Chang

Learning objectives:

- Understand the advantages and challenges of using register-based studies to assess cardiovascular risks in ADHD.
- Learn about three key study designs for pharmacoepidemiological research:
  - Within-individual comparison
  - Nested case-control study
  - Target trial emulation
- Compare the strengths and limitations of these study designs in real-world data analysis.
- Explore how different study designs impact the interpretation of ADHD medication safety findings.
- Recognize practical and clinical considerations when selecting the most appropriate study design for register-based research.

Main content:

- Comparing study designs: RCTs vs. observational studies in pharmacoepidemiology
- Comparison of the three study designs: Key takeaways for researchers.
- Practical and clinical considerations: Choosing the right study design based on research questions, data availability, and clinical relevance.

Scientific reading material (open access):

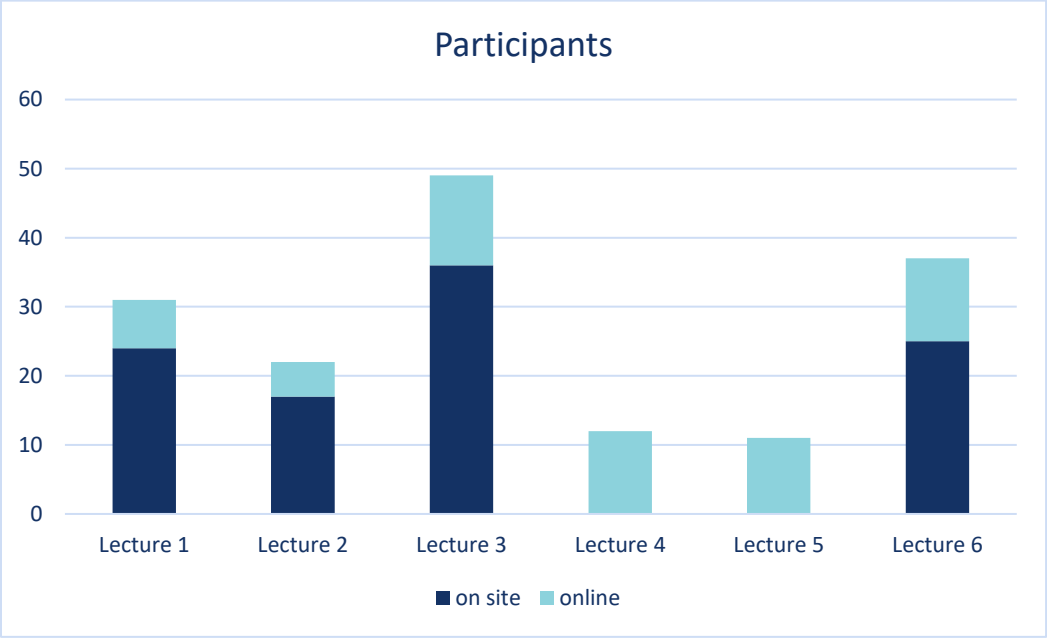
- Garcia-Argibay M, Bürkner P, Lichtenstein P, et al. Methylphenidate and Short-Term Cardiovascular Risk. *JAMA Netw Open*. 2024;7(3):e241349. doi:10.1001/jamanetworkopen.2024.1349
- Li L, Zhu N, Zhang L, et al. ADHD Pharmacotherapy and Mortality in Individuals With ADHD. *JAMA*. 2024;331(10):850–860. doi:10.1001/jama.2024.0851
- Zhang L, Li L, Andell P, et al. Attention-Deficit/Hyperactivity Disorder Medications and Long-Term Risk of Cardiovascular Diseases. *JAMA Psychiatry*. 2024;81(2):178–187. doi:10.1001/jamapsychiatry.2023.4294

2.1.5. Evaluation

Evaluating the training course presents some challenges, as it was not delivered on a single day but developed and conducted over the course of the project. Instead of a traditional evaluation format, we assess its reach and impact by participant numbers, video views (where available), and direct feedback from attendees. The following sections provide an overview of these key metrics and insights from participant evaluations.

Participation

	Lecture 1: 1st Masterclass	Lecture 2: 2nd Masterclass	Lecture 3: 1st Keynote	Lecture 3	Lecture 4	Lecture 5 3rd Masterclass
on site	24	17	36	N/A	N/A	25
online	7	5	13	12[1]	11[1]	12



Attendee Feedback

To evaluate the effectiveness of the training course lectures, participants provided feedback on various aspects of lectures 1, 2, and 6. The visual representations of their responses are shown in Figure 1 to Figure 3.

Responses were collected on a scale from 1 to 5, with 1 meaning "strongly disagree" and 5 meaning "strongly agree."

Overall, the feedback was highly positive, indicating that the lectures were well-received and provided valuable insights. Below is a summary of the key findings:

[1] Date of data extraction: 1st December 2024

- **Relevance of Topics**: Participants found the topics highly relevant, with all three lectures receiving strong ratings (4.2–4.4).
- **Appropriate Duration**: The length of each lecture was well-received, with scores ranging from 4.1 to 4.6, indicating that most attendees felt the timing was appropriate.
- **Learning Experience**: While all lectures were rated positively in terms of knowledge gained (3.9–4.6), Lecture 2 stood out with the highest learning score (4.6).
- **Future Attendance**: Interest in future masterclasses was very high, with all three sessions scoring between 4.4 and 4.9, highlighting strong engagement and participant satisfaction.
- **Opportunity for Discussion**: The availability of time for questions and discussions was well-rated in the two sessions where it was assessed (4.6–4.7), suggesting that participants felt they had sufficient opportunity to engage with the speakers.

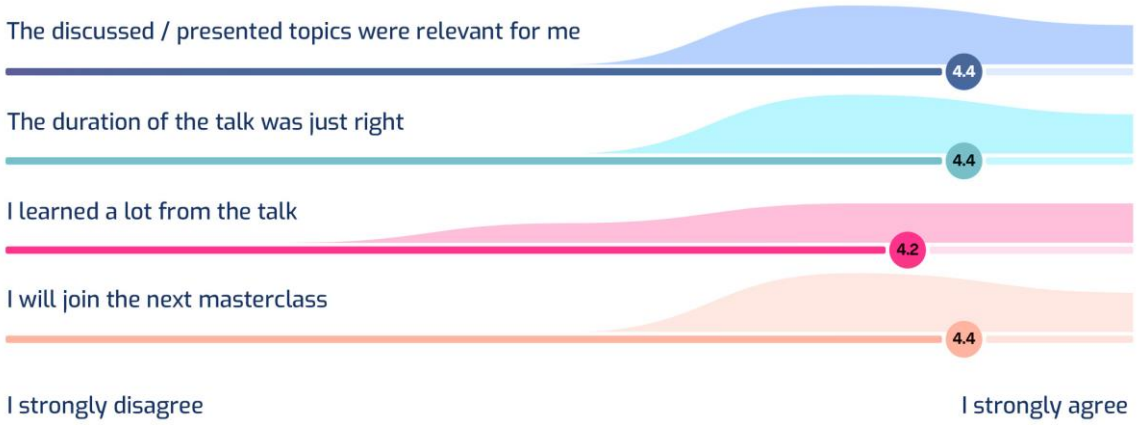


Figure 1: Visualization of participant's feedback Lecture 1: Pharmaco-epidemiology and big (real world) data, by Prof. Dr. Henrik Larsson.

Figure 2: Visualization of participant's feedback on Lecture 2: What can family data tell us about unmeasured confounding? by Ralf Kuja-Halkola, PhD

Figure 3: Visualization of participant's feedback on Lecture 6: Studies of cardiovascular risk in ADHD using registers - Clinical and practical considerations, provided by Prof. Dr. Henrik Larsson and Dr. Zheng Chang

2.2. Deviations from work plan

As task 9: Training and mentorship of work package 8, describes the task at hand as follows: "We will organize a course in pharmaco-epidemiological analyses using real-world data for relevant stakeholders, including scientists linked to pharmaco-epidemiological networks across the world (e.g., the International Society of Pharmacovigilance)." The training course comprising 6 lectures is targeted towards early-career researchers in epidemiology and public health, clinicians and healthcare professionals, students interested in pharmacoepidemiology, and policymakers working on medication safety and healthcare guidelines, we report no deviations from the work plan.

2.3. Contributions to other work packages

The TIMESPAN training course in pharmacoepidemiology contributed to the project beyond its core work package. A key aspect was the engagement of Early Career Scientists across all TIMESPAN work packages, equipping them with essential methodological skills applicable to their research. Additionally, senior researchers from multiple WPs attended sessions, fostering interdisciplinary learning and collaboration across different areas of the project. The course also provided methodological insights directly relevant to work packages focusing on epidemiology, treatment patterns, and predictive modelling.

Furthermore, the integration of two lectures into the ECNP Course on Body and Brain, organized in partnership with the PRIME and CANDY consortia (grant agreement No. 847879 and 847818, respectively), strengthened cross-consortia collaboration, ensuring a broader reach of TIMESPAN's research. This exchange not only enhanced the educational value of the training but also promoted synergy between European research initiatives investigating ADHD and its comorbidities.

3. Conclusion

The TIMESPAN training course in pharmacoepidemiology successfully provided researchers, particularly Early Career Scientists, with essential knowledge and skills to analyse real-world data in the context of ADHD and cardiometabolic health. By covering key epidemiological and methodological principles, the course strengthened participants' ability to apply advanced pharmacoepidemiological approaches within their respective work packages.

Beyond its educational impact, the course fostered interdisciplinary collaboration by engaging researchers across TIMESPAN, facilitating knowledge exchange between work packages, and contributing to broader scientific discussions through its integration into the ECNP Course on Body and Brain.

By making the course materials openly accessible, TIMESPAN ensures lasting value beyond the project's duration, equipping future researchers with the necessary tools to advance ADHD and pharmacoepidemiology research.