Supplementary material

A risk prediction model for cardiovascular diseases in adults initiating pharmacological treatment for Attention-deficit/Hyperactivity Disorder

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Content:

Dobrosavljevic M, *et al. Evid Based Ment Health* 2022;0:1–6. doi: 10.1136/ebmental-2022-300492

Appendix A: List of candidate predictors

Traditional risk factors			Non-traditional risk factors		
	Variable	Data source and type		Variable	Data source and type
1	Age	Total population register, continuous (years of age at treatment initiation)	9	Anxiety	National patient register, Binary, ICD-8,9,10 codes
2	Sex	Total population register, binary (male/female)	10	Depression	
3	Hypertension	National patient register, Binary, ICD-8,9,10 codes, and Prescribed drug register, Binary, ATC codes	11	Bipolar disorder	
4	Type 1 and Type 2 Diabetes mellitus		12	Schizophrenia-spectrum disorders	
			13	Sleep disorders	
5	Hyperlipidemia		14	Alcohol use disorder	
			15	Substance use disorder other than tobacco and alcohol	
6	Obesity	National patient register, Binary, ICD-8,9,10 codes	16	Educational attainment	LISA, Binary, High (0): secondary, post-secondary/university education; and low (1): in/complete elementary school
7	Tobacco use disorder				
8	Family history of CVD (first degree relatives before age 60)		17	Country of origin	Total population register, Non-Swedish/Swedish born
			18	Other psychotropic medication*	Prescribed drug register, Binary, ATC codes

Note: LISA - Longitudinal integration database for health insurance and labour market studies register; ICD – International Classification of Diseases; ATC - Anatomical Therapeutic Classification.
*Each medication from this group will be considered as a separate predictor

Appendix B: International Classification of Diseases (ICD)-8/9/10 codes and the Anatomical Therapeutic Chemical (ATC) Classification System codes for candidate predictors

		ICD-8	ICD-9	ICD-10	ATC
Hypertension		400-404	401-405	I10-I13, I15	C02; C03; C07; C08; C09
Diabetes mellitus		250	250	E10-E14	A10A, A10B
Obesity		277.99	278A, 278B	E65-E66	-
Hyperlipidemia		279	272	E78	C10
Tobacco use disorder		–	305B	F17, T65.2, Z71.6, Z72.0	-
Personal and family history of CVDs*		410-414, 430-438, 451.00, 451.98, 451.99, 450, 427.00, , 427.92, 427.90, 427.91	410-414, 430-438, 451, 415B, 428, 427D, 427A, 427B, 427E, 427F	I20-I25, I60-I69, I80, I26, I50, I48, I47.1, I47.0, I47.2, I49.0, I49.8, I46	-
Anxiety		300 (except 300.4)	300 (except 300E)	F40, F41, F42, F44, F45, F48	
Depression		296.0, 300.4	296B, 300E, 311	F32, F33, F34.1, F34.8, F34.9, F38.1	
Bipolar disorder		296.10, 296.30, 296.80	296A/C/D/E/W	F30–F31	
Schizophrenia		295.00–295.40, 295.60, 295.80–295.90	295A–295E, 295G, 295W, 295X	F20	
Substance use disorder	All (except smoking)	303, 304	303, 304, 305 (except 305B)	F10 – F19 (except F17)	
	Alcohol	303	303, 305A	F10	
	Other substances	304	304, 305X	F11-F19, except F17	

Sleep disorders	347, 780.60	347, 780F	G47.0/1/2/3/4/8/9, F51	
	ATC			
Anxiolytics	N05B			
Hypnotics and sedatives	N05C			
Antiepileptics	N03A, except N03AG01, N03AX09, N03AF01, N03AF02			
Antidepressants	N06A			
Mood stabilizers	N03AG01, N03AX09, N03AF01, N03AF02, N05AN01			
Antipsychotics	N05A, except N05AN01			
Drugs used for addictive disorders (alcohol and opioid dependance)	N07BB01, N07BB03, N07BB04, N02AE01, N07BC01, N07BC02, N07BC51			

*Definition of personal history of CVDs includes medication for CVD (see table Appendix C) in addition to ICD 8/9/10 codes

Appendix C: International Classification of Diseases (ICD)-10 codes and the Anatomical Therapeutic Chemical (ATC) Classification System codes for outcomes

	ICD-10	ATC
Ischemic heart disease		C01D
Acute myocardial infarction	I21-I23 (primary)	
Acute myocardial infarction (also including secondary, type-2 myocardial infarction)	I21-I23 (primary or secondary)	
Acute coronary syndrome	I21-I23 or I20.0	
Any ischemic heart disease (Chronic ischemic heart disease)	I20-I25 (primary or secondary)	
Cerebrovascular disease		–
Subarachnoidal bleeding	I60 (primary or secondary)	
Hemorrhagic stroke	I61-I62 (primary or secondary)	
Ischemic stroke	I63-I64 (primary or secondary)	
Other cerebrovascular disease	I65-I69 (primary or secondary)	
Venous thrombo-embolism		-
Deep vein thrombosis	I80 (primary or secondary)	
Pulmonary emboli	I26 (primary or secondary)	

Heart failure		C01A
Heart failure	I50 (primary diagnosis)	
Heart failure	I50 (primary and secondary)	
Takyarrhythmias		
Atrial fibrillation/fludder	I48 (primary or secondary)	C01A
Supraventricular tachycardia	I47.1 (primary or secondary)	C01B
Ventricular tachycardia	I47.0, I47.2, I49.0, I49.8 (primary or secondary)	
Cardiac arrest	I46 (primary or secondary)	-

*Uncommonly used substances in cardiology

Appendix D: Process of predictors selection

Variables were excluded consecutively based on their p-values: a variable with the highest p-value was excluded in each step of the analysis until all remaining predictors had p-vales lower than 0.1.

Step.	Excluded predictor	estimate	std.error	statistic	df	p.value
1.	Hypnotics and sedatives	-0.00	0.12	-0.01	387.98	0.99
2.	Anxiety	0.03	0.11	0.27	388.98	0.78
3.	Schizophrenia	-0.10	0.32	-0.32	389.98	0.74
4.	Country of origin	-0.07	0.17	-0.42	390.98	0.67
5.	Depression	-0.06	0.11	-0.53	391.98	0.60
6.	Alcohol use disorder	0.08	0.13	0.62	392.98	0.54
7.	Sleep disorders	-0.12	0.18	-0.64	393.98	0.52
8.	Bipolar disorder	-0.16	0.18	-0.92	394.97	0.36
9.	Educational attainment	0.14	0.11	1.29	393.01	0.20
10.	Antiepileptics	0.15	0.12	1.23	396.97	0.22
11.	Antidepressants	-0.18	0.12	-1.51	397.97	0.13
12.	Anxiolytics	0.15	0.11	1.41	398.97	0.16

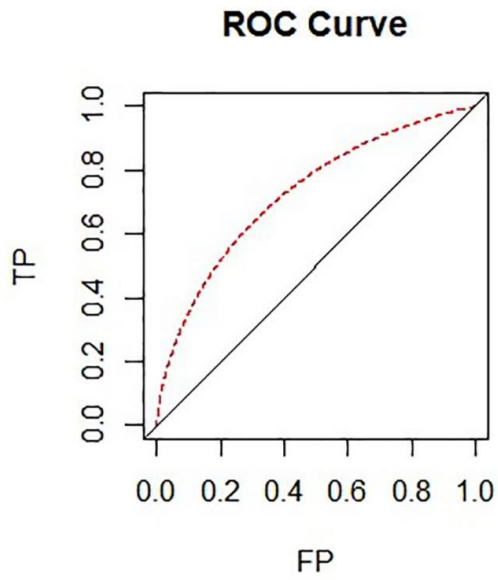
Appendix E: Baseline characteristics of the population with regards to predictors

	Predictor	Total N=24,186	Male N=13,113	Female N=11,073	Individuals with CVD N=413
1	Age at treatment start: median (IQR)	33 (25-42)	32 (25-42)	33 (25-42)	43 (32-51)
		N (%)			
2	Sex (female)	11,073 (45.78%)	-	-	169 (40.92)
3	Hypertension	2956 (12.22)	1355 (10.33)	1601 (14.46)	119 (28.81)
4	Diabetes mellitus (type 1 and 2)	645 (2.67)	362 (2.76)	283 (2.56)	37 (8.96)
5	Obesity	901 (3.73)	278 (2.12)	623 (5.63)	25 (6.05)
6	Hyperlipidaemia	718 (2.97)	411 (3.13)	307 (2.77)	33 (7.99)
7	Tobacco use disorder	309 (1.28)	132 (1.01)	177 (1.60)	13 (3.15)
8	Family history of CVD (before age 60)	4915 (20.32)	2637 (20.11)	2278 (20.57)	98 (23.73)
9	Low educational attainment*	8538 (36.11)	5054 (39.55)	3484 (32.08)	140 (34.15)
10	Born in a country other than Sweden*	2332 (9.64)	1321 (10.07)	1011 (9.13)	38 (9.20)
11	Anxiety	8803 (36.40)	4031 (30.74)	4772 (43.10)	170 (41.16)
12	Depression	8478 (35.05)	3936 (30.01)	4542 (41.02)	158 (38.26)
13	Bipolar disorder	2157 (8.92)	824 (6.28)	1333 (12.04)	47 (11.38)
14	Schizophrenia	343 (1.42)	242 (1.85)	101 (0.91)	11 (2.66)
15	Alcohol use disorder	4769 (19.72)	2961 (22.58)	1808 (16.33)	128 (30.99)
16	Other substances use disorder	6031 (24.93)	3861 (29.44)	2179 (19.60)	162 (39.23)
17	Sleep disorders	1620 (6.70)	928 (7.08)	692 (6.25)	33 (7.99)
18	Anxiolytics	12,113 (50.08)	5743 (43.79)	6370 (57.53)	252 (61.02)
19	Hypnotics and sedatives	12,301 (50.86)	6125 (46.71)	6176 (55.78)	252 (61.02)
20	Antiepileptics	3627 (15.00)	1804 (13.76)	1823 (16.46)	101 (24.46)
21	Antidepressants	16,121 (66.65)	7733 (58.97)	8389 (75.76)	289 (69.98)
22	Mood stabilizers	3864 (15.98)	1792 (13.66)	2072 (18.71)	100 (24.21)

23	Antipsychotics	5609 (23.19)	3010 (22.95)	2599 (23.47)	141 (34.14)
24	Drugs used for addictive disorders (alcohol and opioid dependance)	2778 (11.49)	1816 (13.85)	962 (8.69)	88 (21.31)

*Missing data: Education category, N=545; Country of origin, N=4. Multiple imputation for missing data with 20 imputations were used.

Appendix F: Cardiovascular risk prediction model discrimination shown by the receiver-operating characteristics (ROC) curve, with the false positive rate (1-specificity) on the x-axis and the true positive rate (sensitivity) on the y-axis.



Note: TP-true positive, FP-false positive; The dotted line in red represents the ROC curve achieved by the model with the area under the curve (AUC)=0.73 (95% CI 0.71, 0.75), 0.72 (95% CI 0.70, 0.74) corrected for optimism; The solid line in black represents the ROC curves when AUC equals 50%.

Appendix G: Confusion matrices for two prespecified thresholds and Model 1 (traditional CVD risk factors only) and Model 2 (with added non-traditional CVD risk factors) based on 200 bootstrap samples

Threshold	**Model 1**	Reference		**Model 2**	Reference	
		Non-event	Event		Non-event	Event

20%	Predicted values	Non-event	TN: 11,749	FN: 263	Predicted values	Non-event	TN: 11,608	FN: 249
		Event	FP: 1204	TP: 160		Event	FP: 1345	TP: 174
10%			Non-event	Event			Non-event	Event
	Predicted values	Non-event	TN: 8567	FN: 140	Predicted values	Non-event	TN: 8630	FN: 125
		Event	FP: 4386	TP: 283		Event	FP: 4323	TP: 298

Note: TN: true negative; FN: false negative; FP: false positive; TP: true positive

Appendix H: Study protocol

Study summary

Design: Retrospective cohort study

Data sources: Data on ICD-based diagnoses and ATC-based medication prescriptions will be merged from several Swedish national registers.

Population and study period: We will follow all individuals aged 18 and older who initiate pharmacological treatment for ADHD between January 1st, 2008 and December 31st, 2011, from the date of treatment initiation until a cardiovascular disorder (CVD) diagnosis, emigration, death, or the end of two years, which ever came first.

Risk factors: We will include relevant traditional risk factors (age, sex, history of hypertension, diabetes mellitus, obesity, hyperlipidaemia, tobacco use disorder, and family history of CVDs), psychiatric disorders (history of depression, anxiety, alcohol use disorder, substance use disorder other than alcohol and tobacco, bipolar disorder, schizophrenia), previous use of other nervous system acting drugs, educational attainment, and country of origin.

Outcomes: First diagnosis of CVD after ADHD treatment initiation in the period between January 1st, 2008 and December 31st, 2011, within a two-year period.

Outputs: The main aim of the current study is to create a two-year risk model that will estimate the probability of obtaining a diagnosis of CVDs, with appropriate measures of predictive accuracy, and to obtain a scoring system for the calculation of risk at the time of ADHD treatment initiation.

Methods

Data sources

Data from multiple Swedish national registers will be merged, including the National Patient Register (NPR), Cause of Death Register (CDR), Prescribed Drug Register (PDR), and Longitudinal integration database for health insurance and labour market studies register (LISA). All diagnoses in the NPR and CDR were classified according to the International Classification of Diseases (ICD) versions 7/8/9/10. The Prescribed Drug Register (PDR) covers data on all dispensed medication prescriptions since July 1st, 2005, until December 31st, 2013, using the Anatomical Therapeutic Classification (ATC) system, with a date of prescription and dosage. Individuals from our study population will be linked with their first-degree relatives (parents and full siblings) using the Multi-generation Register, and information on family history of CVDs will be extracted from the NPR.

Population and study period

Our cohort will be consisted of individuals aged ≥ 18 and born between 1932 and 1990, who had started pharmacological treatment for ADHD (Zetterqvist et al., 2013) between January 1st, 2008 and December 31st, 2011, and without previous history of CVDs. The inclusion period starts on January 1st, 2008, to allow for a wash-out period of two years for previous ADHD medication prescription, and previous prescriptions for other medication considered in the model. The inclusion period ends with December 31st, 2011, to allow for a two-year follow up, since the last available date of access for the study authors in the registers is December 31st, 2013. Individuals from the cohort will be followed from the starting date of the treatment until they developed a diagnosis of CVD, emigrated from Sweden, died, or by the end of two years.

We will include individuals with dispensed medication prescriptions for the following: Amphetamine (ATC code N06BA01), Dexamphetamine (ATC code N06BA02), and Methylphenidate (ATC code

N06BA04), and non-stimulant medication: Atomoxetine (ATC code N06BA09). Medication prescriptions for ADHD will be acquired from derived data based on natural language processing models for free-text prescriptions from the PDR, including medication prescription between 2006 and 2013 (Zhang et al., 2021). Prescriptions that were returned to pharmacies by patients after dispensation will be removed from the analysis. Furthermore, prescriptions for indications other than ADHD (e.g., narcolepsy, multiple sclerosis, idiopathic hypersomnia, and myotonic dystrophy) will be excluded from the analysis.

Candidate predictors

Previous well established risk prediction models for coronary heart disease include traditional risk factors such as: hypertension/hypertensive therapy, body mass index (BMI), smoking, diabetes, total/LDL/HDL cholesterol (Wilson et al., 1998) and family history of CVDs (Tunstall-Pedoe et al., 1997). We will select predictors a priori, based on previously established risk prediction models and relevant literature (i.e., systematic reviews and meta-analyses when available) and expert opinion. We will consider relevant somatic disorders, psychiatric disorders, and low educational attainment, associated with an increased risk for CVDs (Hennekens et al., 2005; Cohen et al., 2015; Kubota et al., 2017), which are also potential outcomes of ADHD (Nigg, 2013; Kooij et al., 2019); and previous use of nervous system acting drugs other than ADHD medication, which are commonly used for treatment of ADHD comorbidities and which have been associated with an increased risk for CVDs (Correll et al., 2015). All relevant diagnoses, medication prescriptions and socio-demographic information will be acquired by the date of first ADHD medication prescription.

We will include traditional CVD risk factors which are available in Swedish health registers: age, sex, a diagnosis of hypertension, diabetes mellitus, hyperlipidaemia, obesity, and smoking and family history of CVDs before age 60.

Non-traditional risk factors that will be considered are variables with prior evidence of associations with CVDs and/or ADHD: psychiatric disorders (i.e., depression, anxiety, alcohol use disorder, substance use disorder other than alcohol and tobacco, schizophrenia, bipolar disorder), previous use of other central nervous system agents (anxiolytics, antidepressants, hypnotics and sedatives, antiepileptics, mood stabilizers, antipsychotics and drugs used for addictive disorders), and demographic variables: educational attainment and country of origin (Sweden and other than Sweden). Anxiolytics may be used as a cardiovascular protective agent (Grundy et al., 2004; Balon et al., 2018), although some studies report an increased risk for cardiovascular-related death associated with the use of anxiolytics, and hypnotics and sedatives, combined with analgesics (Merlo et al., 1996), and an increased risk for a CVD event, associated with a combined used of antidepressants and anxiolytics (Krantz et al., 2009).

The model will use a backwards stepwise procedure to determine whether to retain these predictors based on their p-values (variables with the highest p value from the group of non-traditional risk

factors will be sequentially rejected, until none of them remain with a p-value greater than 0.1) (Royston and Sauerbrei, 2008), while holding fixed traditional risk factors.

The final model must present face validity. Interactions between predictors will not be considered in the model.

Outcomes

We will include an incident diagnosis (i.e., primary or any secondary diagnosis) or treatment prescription of the following CVDs: ischemic heart disease, cerebrovascular disease, venous thrombo-embolism, heart failure and tachyarrhythmias, after ADHD treatment initiation and within a two-year period. Cases of CVDs will be defined based on ICD-10 diagnostic codes from the NPR and CDR (Appendix B). We will include CVD medication prescription based on ATC codes from the PDR (Appendix B), to increase the coverage of cases, given that CVD conditions are often diagnosed and followed-up in primary care services and are, therefore, not covered by the NPR, which only includes specialist services. Medications used as secondary prevention of CVDs will not be considered, but only those used specifically for treatment of included CVDs.

Statistical analysis

We will apply Cox proportional hazards regression analysis to assess the association between CVDs and candidate predictors. A bootstrapping method will be used for internal validation of the model with 200 bootstrap samples. To assess discrimination of the model, ROC curve and c-index will be used. To assess calibration of the model we will use the Brier score (Brier, 1950) and calibration plots (by assessing the proportion of predicted and observed events at different levels of predicted probability) (Harrell et al., 1982). We will present sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) across two high-risk thresholds of predicted probability set at 10% from a 5-year CVD risk prediction model (Polonsky et al., 2010) and 20% from a 10-year model (Grundy et al., 2004).

We will also compare the performance of the model that includes only traditional risk factors with the model which includes additional non-traditional risk factors by calculating the following measurers of incremental value: the Net Reclassification Index (NRI), which summarizes reclassification of participants when new predictors are added based on the two predefined thresholds of predicted probability; two category-free or continuous measures: the category-free NRI (Pencina et al., 2008; Steyerberg et al., 2012) and the Integrated Discrimination Improvement (IDI) index (Kerr et al., 2011), which cover all possible cut-offs or thresholds of predicted probability.

Missing data

If less than 30% of data is missing at random, we will use multiple imputation with 20 imputations using a regression model with all candidate predictors as explanatory variables and the outcome variable (White and Royston, 2009; Bartlett et al., 2015). Otherwise, the predictor will be excluded from the model. We will fit the analysis in each imputed data set and combined parameter estimates using Rubin's rule.

Presentation of findings and model generalizability

The main output of the model will be a predictive probability of occurrence of CVD from the date of ADHD pharmacological treatment initiation, within a two-year time-window. All risk factors and their estimated coefficients will be examined to create a model with face validity, and which is easy to use in practice (most of the predictors are binary). Considered candidate predictors should be easily assessed in clinical setting (i.e., medical history, medical examination, psychiatric assessment, etc.).

Changes in the protocol after study completion: To increase the participant coverage for the following predictors: hypertension, hyperlipidaemia, and diabetes mellitus (type 1 and 2), we additionally used dispensed medications for these conditions to identify affected individuals (see Appendix B for ATC codes). We also limited family history of CVD to only those individuals whose first-degree relatives acquired a CVD diagnosis before age 60, as it has been done in traditional CVD prediction models (Tunstall-Pedoe et al., 1997; Hippisley-Cox et al., 2017).

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Appendix J. Post hoc analyses (analyses not prespecified by study protocol)

1) Performance of the derived model across different subgroups

	N	CVD cases	C-index with 95% CI	Brier score
Sex				
Male	13,113	244	0.75 (0.72, 0.78)	0.009
Female	11,073	169	0.71 (0.67, 0.75)	0.007
Medication				

Stimulant	20,462	345	0.73 (0.70, 0.76)	0.008
Nonstimulant	3724	68	0.74 (0.69, 0.79)	0.009
Age group				
Younger than 40	16,655	169	0.68 (0.64, 0.72)	0.005
Aged 40 and older	7531	244	0.70 (0.67, 0.73)	0.015

Note. CI: confidence interval

2) Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and net reclassification index (NRI) for a model containing traditional risk factors only (Model 1), and a derived model containing both traditional and novel risk factors (Model 2) across different percentile risk thresholds

Percentile	Model	Cutoff	Sensitivity	Specificity	PPV	NPV	NRI, 95% CI
95th	1	27.0%	0.20	0.95	0.12	0.97	0.004 (-0.005, 0.019)
	2	28.6%	0.21	0.95	0.13	0.97	
90th	1	20.2%	0.34	0.91	0.11	0.98	0.01 (-0.01, 0.02)
	2	21.1%	0.34	0.91	0.11	0.98	
80th	1	14.3%	0.48	0.81	0.07	0.98	-0.003 (-0.019, 0.0189
	2	14.7%	0.52	0.81	0.08	0.98	
50th	1	7.1%	0.75	0.51	0.05	0.98	0.001 (-0.025, 0.032)
	2	7.4%	0.78	0.51	0.05	0.99	

Note. CI: confidence interval